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Archives of Internal Medicine

VOLUME 52 OCTOBER, 1933 NUMBER 4

PRIMARY CARCINOMA OF THE LUNG

WITH SPECIAL REFERENCE TO INCIDENCE, EARLY DIAGNOSIS AND TREATMENT

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Owing to the rather large number of recent reports on primary cancer of the lung, another contribution may seem to be an unnecessary addition to the already extensive literature. As we review this subject and reflect on past experiences, we suspect that many cases may have been overlooked owing to a lack of complete understanding or an inadequate study of the material. Particularly was this true a decade or more ago when the disease appeared to be more or less a rarity. Recently there has been a reported increase in cancer of the lung to a figure approaching 2 per cent of all patients coming to autopsy. Wells [1] said, "There seems to be little doubt that primary cancer of the lung is now a more common disease in Europe and America than it was even ten or fifteen years ago." The disease appears to be so common that it behooves every clinician, especially those dealing with conditions of the chest, to keep it constantly in mind. It is therefore because of an obvious need of emphasizing the diagnostic criteria of this condition, as well as of pointing out the desirability and feasibility of early treatment, that we feel justified in the present effort.

HISTORY

From a historical standpoint, only outstanding developments need be given for the purpose of a better orientation of the subject. Bayle,[2] in 1810, reported three cases of true cancer of the lung as "phthise cancereuse," and noted diffuse and nodular types. This was the first definite work on cancer of the lung. Laennec,[3] in 1819, led a group

From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium.

1. Wells, H. G.: Cancer Statistics as They Appear to the Pathologist, J. A. M. A. **88**:399 (Feb. 5); 476 (Feb. 12) 1927.

2. Bayle, G. L.: Recherches sur la phthisie pulmonaire, Paris, Gabon, 1810, p. 439.

3. Laennec, R. T. H.: Traité de l'auscultation médiate et des maladies des poumons et du cœur, Paris, J. A. Brosson & J. S. Chaudé, 1819, vol. 2, p. 295.

of men who described "encaphaloid" of the lung, but he was not able to diagnose it ante mortem. Walsche,[4] in 1843, called it by the name "cancer." In the same year Köhler,[5] in Germany, wrote a monograph on the subject. Bell [6] first diagnosed pulmonary cancer in life from the symptoms of dyspnea, cough, pain and stridor and verified it by autopsy. Stokes [7] first diagnosed it by physical examination and gave a complete description of its clinical manifestations. In 1863, Virchow [8] described the pathologic process of pulmonary tumors, including cancer of the lung, although it was his opinion that primary cancers of the lung were rare. Waldeyer,[9] in 1867, showed the origin from epithelium, although a controversy over the squamous or cylindric cell origin arose soon after and has continued to recent times.

INCIDENCE

The incidence of cancer of the lung is a perplexing problem and one about which a variety of opinions exist, many of which are to the effect that it has increased rapidly since the World War. Weller [10] accurately expressed the situation when he said: "No other form of neoplastic disease is more intriguing from the standpoint of incidence than primary carcinoma of the lung, for within a generation it appears to have become one of the common forms of malignant disease instead of the rarity which it was believed to be at the beginning of the century."

The realization of its relative frequency began just prior to the Great War, although various reports have been made from time to time over the last half century. In 1878, Reinhard [11] collected 25 cases of carcinoma of the lung, but by 1891 Werner [12] could find only 9 that were fully verified. Wolf [13] collected 31 in 1895, and Pässler [14] 57 by

4. Walsche, W. H.: A Practical Treatise on Diseases of the Lung, ed. 4, London, Smith, Elder & Co., 1871.

5. Köhler, R., quoted by Wolff, Jacob: Die Lehre von der Krebskrankheit, Jena, G. Fischer, 1911, vol. 2.

6. Bell, J., quoted by Jacob Wolff.[5]

7. Stokes, W.: Diagnosis of Cancers of the Lung and Mediastinum, Dublin M. J. **21**:206, 1842.

8. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863.

9. Waldeyer, A.: Die Entwicklung der Karzinoma, Virchows Arch. f. path. Anat. **41**:470, 1867.

10. Weller, C. V.: Pathology of Primary Carcinoma of the Lung, Arch. Path. **7**:478 (March) 1929.

11. Reinhard, W.: Der primäre Lungenkrebs, Arch. d. Heilk. **19**:369, 1878.

12. Werner, M.: Das primäre Lungencarinom, Freiburg I. B., H. Epstein, 1891; quoted by Weller.

13. Wolf, K.: Der primäre Lungenkrebs, Fortsch. d. Med. **13**:725 and 765, 1895.

14. Pässler, H.: Ueber das primäre Carcinom der Lunge, Virchows Arch. f. path. Anat. **145**:191, 1896.

1896. In 1911, Adler [15] collected 374, and in 1918, McMahon and Carman [16] stated that there were 428, authentic reports. At present there are several thousand reports on record, and the number has been rising so rapidly that the disease is considered by many to be undergoing an increase.

In arriving at definite information concerning the alleged increase of primary cancer of the lung, we may profitably make comparisons with that of cancer in general, because after all cancer of the lung should be governed by the same laws that govern general cancer. Concerning the latter, we find reliable statistics and many carefully prepared reports, one of the best of which is that of Wells.[1] This author, among other things, stated that "A high cancer death rate is evidence of a good state of public health," and again, "Cancer is probably increasing to just about the extent that people are kept from dying of something else." Although Briese,[17] Egenolf,[18] Bejach,[19] Holzer,[20] and others found no increase, it seems probable that a relative increase should exist as a result of, and proportionate to, an increased life expectancy, and that the recorded incidence will increase with diagnostic zeal and acumen. Many pathologists—Junghanns,[21] Hanf,[22] Breckwoldt [23] and Sonnenfeld [24]—however, report increases, and public health agencies are almost unanimous in this opinion.

The records of the United States Census Bureau [25] for the years 1900 to 1914, inclusive, show for a large number of countries a gradual increase (with the exception of Switzerland) from 15 to 40 per cent. This incidentally was a quiet period of the world's history.

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15. Adler, I.: Primary Malignant Growths of the Lungs and Bronchi, New York, Longmans, Green & Company, 1912.

16. McMahon, F. B., and Carman, R. D.: Roentgenologic Diagnosis of Primary Carcinoma of the Lung, Am. J. M. Sc. **155**:34, 1918.

17. Briese: Zur Kenntnis des primären Lungenkarzinoms, mit statistischen Angaben, Frankfurt. Ztschr. f. Path. **23**:48, 1920.

18. Egenolf, W.: Ueber die in den Jahren 1921-1927 vom Göttinger pathologischen Institut beobachteten bösartigen Geschwülste, Ztschr. f. Krebsforsch. **31**:396, 1930.

19. Bejach, H. E.: Beiträge zur Statistik des Carcinomas, Ztschr. f. Krebsforsch. **16**:159, 1917.

20. Holzer, H.: Zur Frage der Häufigkeit des Bronchialkrebses, Med. Klin. **21**:1235, 1925.

21. Junghanns, H.: Der Krebs der Lungen, Bronchien und oberen Luftwege, Ztschr. f. Krebsforsch. **28**:573, 1929.

22. Hanf, Dora: Zur Frage der Zunahme der Lungenkrebse in den letzten Jahren, Virchows Arch. f. path. Anat. **264**:366, 1927.

23. Breckwoldt, R.: Zur Frage der Zunahme der Lungenkrebse, Ztschr. f. Krebsforsch. **23**:128, 1926.

24. Sonnenfeld, A.: Klinik des primären Bronchialcarcinoms, Ergebn. d. ges. Med. **8**:546, 1926.

25. U. S. Census Bureau, Cancer Mortality, 1914, p. 18.

According to Cumming,[26] the death rate from cancer in the United States increased 50 per cent from 1900 to 1929. Lichty and his co-workers [27] showed an increase of about 10 per cent from 1916 to 1925. As Cumming also stated that between 1900 and 1929 there was a decrease in the death rate from 17.195 to 12.343 per thousand population (39.3 per cent) and an increase in life expectancy to 58 years, we may consistently assume with Wells that the number of persons saved from tuberculosis, typhoid, diphtheria, scarlet fever and measles during early and middle life has been added to the number of those attaining the cancer age, and thus the number of deaths from cancer has been increased almost in the same proportion.

The operation of this shifting of the population into the cancer age is shown in figure 1, taken from figures of the United States Census Bureau, one for 1880 and one for 1928—a period of forty-eight years, after which time about twice as many people are shown to reach the

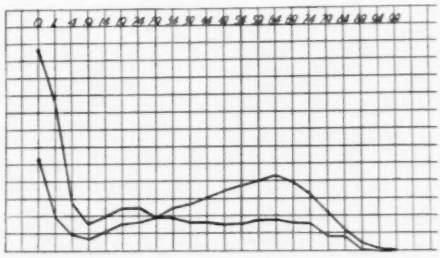

Fig. 1.—Death rate curves for 1880 and 1928, respectively. The curve of 1880 begins high and tapers off gradually toward old age, while the 1928 curve begins lower, drops lowest at about 9 years, crosses the other curve in midlife, and rises to a second peak at 64 years. The people dying formerly in young life are carried over and die in adult life, about twice as many reaching the cancer age.

cancer age as before. This is compatible with an average increase of 24 per cent in cancer in the United States from 1900 to 1914, as revealed by the aforementioned census report.

While one must not be deceived by a decreasing death rate, which may be apparent only as a result of an increased birth rate, the increase in the period of life expectancy is a sure sign of longevity.

In a further attempt to compare cancer of the lung with cancer in general, we have plotted the figures representing most of the larger collections found in German and in English literature that were suitable

26. Cumming, H. S.: Herald-Tribune Magazine, New York, Nov. 1, 1931.

27. Lichty, J. A.; Wright, F. R., and Baumgartner, E. A.: Primary Cancer of the Lung, J. A. M. A. **87**:144 (July 17) 1926.

for charting. Kikuth,[28] Brandt [29] and Biberfeld,[30] among others, have already shown such charts. Three other representative authors have been selected at random when several sets of figures are given at different periods of time, and the findings have been listed in figure 2. *A* shows the findings of Junghanns [21] of Dresden; *B*, those of Assmann [31] of Leipzig, and *C*, those of Holzer [20] of Prague. Three sets of figures have been plotted with three curves each, all of which are explained in the legends. The relatively high figures of two of these (as well as other authors at the beginning of the century) cause us to wonder if the reported increase in cancer of the lung, based on autopsies, may not be due more to human fallibility in diagnosis or some other factor than to a true increase. With these various points in mind, we have

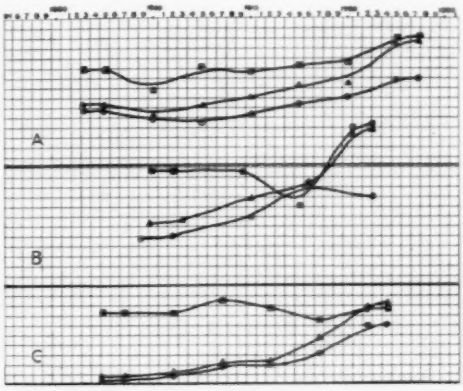

Fig. 2.—Relation of cancer of the lung to general cancer: *A*, findings of Junghann of Dresden; *B*, of Assmann of Leipzig, and *C*, of Holzer of Prague. The curves marked with squares represent the general cancer in percentage of all autopsies; each line rise equals 1 per cent. The curves marked with triangles represent cancer of the lung in tenths of per cent; each line rise equals 0.1 per cent. The curve marked with circles is the percentage ratio of cancer of the lung to cancer in general.

charted in figure 3 approximate curves of twenty-one authors from various parts of the world.

28. Kikuth, W.: Ueber Lungencarcinom, Virchows Arch. f. path. Anat. **255**:107, 1925.

29. Brandt, M.: Ueber primäre Lungentumoren in Riga, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39**:74, 1926.

30. Biberfeld, H.: Zur Statistik und Klinik der Lungengeschwülste, Med. Klin. **22**:1353, 1926.

31. Assmann, H.: Zur Frage der Pathogenese und zur Klinik des Bronchialkarzinoms, Med. Klin. **20**:1757 and 1796, 1924.

In addition to Junghanns [21] and Assmann,[31] Duguid [32] of Manchester, England, Breckwoldt [23] of Hamburg, Katz [33] of Heidelberg and Lipschitz [34] of Zwickau have always obtained rather high results, but reported a further increase nevertheless. Some reveal a depression from about 1912 to 1918 (perhaps due to the war when attention was more or less diverted). Katz,[33] Kikuth,[28] Hanf [22] and Biberfeld [30] showed this depression. Others included are Wolf,[13] Fuchs,[35] Reinhard [11] and Pässler [14] (all before 1895), who showed a very low percentage; Zacherl,[36] who has used some of the same figures presented

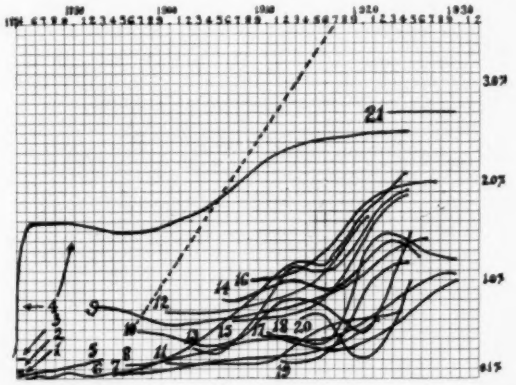

Fig. 3.—Increase in cancer of the lung, expressed in percentage of all autopsies by various men: *1*, Reinhard; *2*, Fuchs; *3*, Wolf; *4*, Duguid; *5*, Pässler; *6*, Kikuth; *7*, Holzer; *8*, Zacherl; *9*, Junghanns; *10*, Biberfeld; *11*, Staehelin; *12*, Seyfarth; *13*, Hanf; *14*, Katz; *15*, Simpson; *16*, Lipschitz; *17*, Berblinger; *18*, Rosaln; *19*, Sonnenfeld; *20*, Breckwoldt, and *21*, Buschbeck. Note the "depression" during the World War and the sharp increase afterward. The heavy broken line represents the improvement in diagnosis, expressed in percentage, as given by Ferenczy and Matolcsy, Weller and Lubarsch for different periods beginning in 1896 with 5 per cent and ending in 1925 with 47.5 per cent correct diagnoses.

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32. Duguid, J. B.: Incidence of Intrathoracic Tumors in Manchester, Lancet **2**:111 (July 16) 1927.

33. Katz, K.: Statistischer Beitrag zur Kenntnis des Lungencarcinoms, Ztschr. f. Krebsforsch. **25**:368, 1927.

34. Lipschitz, M. A.: Ueber die Zunahme des Bronchialkarzinoms im letzten Jahrzehnt, Deutsche med. Wchnschr. **55**:1708, 1929.

35. Fuchs: Beiträge zur Kenntnis der primären Geschwulstbildungen in der Lunge, Inaug. Diss., Munich, 1886; quoted by B. M. Fried.

36. Zacherl, S.: Ueber das primäre Lungenkarzinom, Wien. klin. Wchnschr. **44**:967, 1931.

before by Ferenczy and Matolcsy;[37] Seyfarth,[38] Staehelin,[39] Simpson-Levy,[40] Rosahn,[41] Berblinger[42] and Buschbeck.[43] No pretense is made at completeness, although most of the large collections have been included (fig. 3).

In order to be more absolute, we selected the most important complete sets of figures of European authors for a thirty-four year period, tabulated the total figures by year in the accompanying table and charted them in figure 4. These figures include only complete years, so they

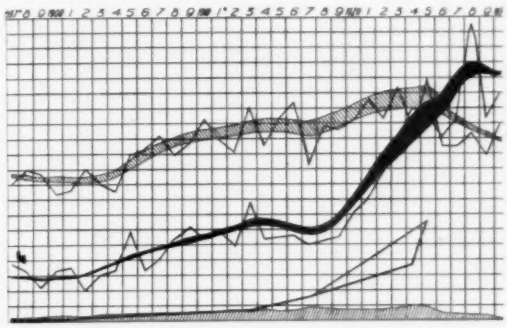

Fig. 4.—The aggregate of general cancer and cancers of the lung (table 1) in the most important complete reports. The top barred band (along the irregular curve) represents the ratio of general cancer to all autopsies (each large square represents 1 per cent). The width of the band represents approximately the number of hundreds for each small square per year. The black band is the same for cancers of the lung except that the quantity is one tenth of the other. The barred band at the bottom represents the total autopsies expressed as thousands for each small square per year. The black curve ending in a triangle represents a few reports expressing the percentage of correct diagnoses of cancers of the lung. It begins at about 5 per cent in 1897 and ends at about 50 per cent in 1925.

37. Ferenczy, K., and Matolcsy, T.: Ueber das primäre Lungenkarzinom, Wien. klin. Wchnschr. **40**:618, 1927.

38. Seyfarth, C.: Lungenkarzinome in Leipzig, Deutsche med. Wchnschr. **50**:1497, 1924.

39. Staehelin, R.: Ueber die Zunahme des primären Lungenkrebses mit Bemerkungen über die Diagnose, Klin. Wchnschr. **4**:1853, 1925.

40. Simpson-Levy, S. L.: Primary Carcinoma of the Lung, Quart. J. Med. **22**:413, 1929.

41. Rosahn, P. D.: Incidence of Primary Carcinoma of the Lung, Am. J. M. Sc. **179**:803, 1930.

42. Berblinger, W.: Zunahme des Lungenkrebses und Staublungenkrankheiten, Med. Klin. **27**:1337, 1931.

43. Buschbeck, H.: Ueber die Häufigkeit des primären Lungencarcinoms, Ztschr. f. Krebsforsch. **34**:678, 1931.

may not coincide exactly with those given in the respective reports. They include 79 cases of Berblinger,[42] 71 of Kuhn,[44] 100 of Katz,[33] 47 of Breckwoldt,[23] 79 of Sonnenfeld,[24] 198 of Biberfeld,[30] 129 of Schlesinger,[45] 245 of Kikuth,[28] 200 of Hanf,[22] 89 of Lipschitz [34] and 136 of Buschbeck.[43]

In all there are 1,355 cancers of the lung and 22,712 cancers in 185,434 autopsies. By adding the redistributed figures of Junghanns,[21]

Aggregate Figures of Important Complete Reports of Cancers, Cancers of the Lung and Total Autopsies from 1897 to 1930, Inclusive

Year	Total Number of Autopsies	Total Number of Cancers	Percentage of Cancers in Relation to All Autopsies	Total Number of Cancers of Lungs and Bronchi	Percentage of Cancers of Lungs and Bronchi in Relation to	
					All Cancers	All Autopsies
1897	2,417	218	9.0	9	4.1	0.38
1898	2,700	270	10.0	9	3.3	0.33
1899	2,800	270	9.7	6	2.2	0.22
1900	3,406	283	8.3	11	3.8	0.33
1901	3,084	266	8.6	11	4.0	0.35
1902	3,000	300	10.0	6	2.0	0.20
1903	4,278	387	9.0	13	3.4	0.30
1904	4,198	355	8.5	14	3.9	0.33
1905	4,459	488	10.9	17	3.5	0.38
1906	4,829	543	11.3	16	2.9	0.33
1907	5,019	613	12.2	20	3.2	0.40
1908	4,934	542	10.9	27	5.0	0.54
1909	5,481	641	11.7	34	5.3	0.62
1910	5,713	758	13.3	39	4.0	0.68
1911	6,156	734	11.9	37	5.0	0.58
1912	6,693	743	11.1	33	4.5	0.49
1913	5,784	816	14.1	45	5.5	0.78
1914	7,403	851	11.5	40	4.7	0.54
1915	6,021	804	13.3	35	4.2	0.55
1916	6,683	963	14.4	37	3.9	0.56
1917	8,848	899	10.2	33	3.7	0.50
1918	8,006	1,026	12.8	50	4.8	0.62
1919	7,212	908	12.6	40	4.4	0.56
1920	7,154	943	13.2	51	5.4	0.72
1921	7,049	1,030	14.6	56	5.4	0.80
1922	7,298	1,072	13.3	71	7.0	0.98
1923	8,191	1,266	15.4	98	7.7	1.19
1924	9,809	1,227	12.5	102	8.3	1.40
1925	8,858	1,404	15.9	130	9.2	1.50
1926	4,805	551	11.5	58	10.6	1.21
1927	4,558	524	11.5	67	12.9	1.47
1928	3,776	467	12.4	74	16.0	1.96
1929	3,546	384	10.9	47	12.3	1.33
1930	1,266	166	13.0	19	11.4	1.50
Total	185,434	22,712	12.2	1,355		

Probst,[46] Holzer,[20] Derischanoff [47] and Zacherl,[36] who gave the numbers in five year periods, the results were almost identical, giving a total

44. Kuhn, C.: Symptomatologie des primären Bronchialcarcinoms, Ztschr. f. Krebsforsch. **31**:276, 1930.

45. Schlesinger, M.: Bronchialcarcinome von 1924-1929, in Leipzig, Ztschr. f. Krebsforsch. **31**:517, 1931.

46. Probst, R.: Häufigkeit des Lungencarcinoms, Ztschr. f. Krebsforsch. **25**:431, 1927.

47. Derischanoff, S.: Zur Statistik und Genese des Lungenkrebses, Ztschr. f. Krebsforsch. **35**:481, 1932.

of 2,359 cancers of the lung and 38,338 cancers in 359,389 autopsies, perhaps half of all cancers of the lung reported to date.

These figures and charts reveal a gradually increasing incidence of general cancer of around 65 per cent over the thirty-four years with a depression during and after the war. There is also an increasing incidence of cancer of the lung that is greater than the incidence of general cancer until the war; then, after a slight depression, there is a tremendous rise, the peak being reached in 1928, amounting to a tenfold increase. Since then there has been a tendency to decrease. Corresponding to this rise, however, is an increase in the diagnoses of cancer of the lung, as given by certain authors, from 5 per cent in 1896 to about 50 per cent in 1925. With careful work, it should approach 75 per cent at the present time. General cancer is entirely different. The diagnosis in this group should have been well over half correct throughout the whole thirty-four year period. Instead of a tenfold increase in diagnoses, as with cancer of the lung, there is no more than a 10 or 15 per cent increase.

It may be contended that an increase in diagnoses should have no effect on figures based on autopsies, but it will tend to bring more cancers of the lung to autopsy and to increase the figures based on autopsies at the expense of the greater group of cancers of the lung that do not come to autopsy. Furthermore, the tendency to more hospitalization, better transportation, better training of physicians during the war and a better appreciation of medical aid on the part of the returned soldiers will increase the recorded incidence without affecting the true incidence of cancer of the lung.

The causes of the increase in diagnosis of cancer of the lung are many and variable. In this regard, one must bear in mind that the discovery of the tubercle bacillus in 1882 permitted a vast number of patients to be separated from those definitely tuberculous and has made further search for diagnosis necessary. It has been our observation that tubercle bacilli are found in all but a trivial minority of active, advanced cases of pulmonary tuberculosis.

The discovery of the x-rays in 1896, with their far-reaching application in medical diagnosis in the last twenty years, has also established the diagnosis of cancer of the lung in many patients whose disease would otherwise have been classed as some other condition.

The use of opaque substances (iodized poppy seed oil 40 per cent), bronchoscopy, pneumothorax, thoracoscopy and bronchoscopic section have all added to diagnostic equipment until over 75 per cent of the diagnoses of cancer of the lung today are, or should be, correct, while less than a decade ago Staehelin,[39] Kikuth,[28] Wells,[1] Grove and Kramer [48] and

48. Grove, J. S., and Kramer, S. E.: Primary Carcinoma of the Lung, Am. J. M. Sc. **171**:250, 1926.

others reported not over 35 per cent correct diagnoses. Ferenczy and Matolcsy [47] reported 5 per cent correct diagnoses from 1896 to 1900, 28.4 per cent from 1917 to 1925 and 50 per cent in 1925. In Lubarsch's series, the correct diagnoses totaled 52 per cent in 1920. In 1913, Weller reported only 11 per cent in a collected series of 90 cases. These figures show a marked improvement in diagnosis as years go by.

This same principle applies to nearly all internal or "inaccessible" cancers, although the incidence of external cancers has changed little—in fact, the death rate from external cancer has decreased.

More important than any other factors, however, is the change in pathologic diagnoses. Pathologists have varied their attitude toward the nature of cancer of the lung, thereby placing many cases in this group that were formerly considered to be some other condition. As pointed out by Fried,[49] a dictum of Virchow pervaded the field for a long time. Virchow was of the opinion that the tissue which was subject to metastatic growth rarely produced primary growth, and the lungs were cited as an example. Only a few scattering reports came from the early writers, and perhaps not until Virchow's great influence began to wane did the subject again become open to unbiased investigation. Many of the cancers found in the lungs were formerly considered to be metastases because they are chiefly located at the hilus, where metastases commonly occur. Many were also considered as mediastinal tumors.

One of the greatest changes, however, from the pathologists' point of view, was due to a better understanding of the origin of the undifferentiated cells in cancer of the lung, many of which were formerly considered sarcomatous.

Some of the small cell and even the "oat cell" types may have been considered as sarcomas. In Hunt's [50] series of 26 cases, 21 were of the "oat cell" type. Then many were perhaps considered mediastinal tumors (lymphosarcomas, thymomas and similar tumors) without careful histopathologic analysis. So one sees that it is not only an improvement in diagnoses, but the change of erroneous diagnoses in a relatively small group of cases that come to autopsy that may well have produced a tremendous change in the apparent incidence of cancer of the lung.

ETIOLOGY

Only slightly less complicated than the problem of the incidence is that of the etiology. About the only thing definite is that the cause seems to be similar to that of cancer elsewhere. A complete analysis

49. Fried, B. M.: Primary Carcinoma of the Lung, Medicine **10**:373, 1931.
50. Hunt, T. C.: Pulmonary Neoplasms, Lancet **1**:759 (April 13) 1929.

of the etiology of cancer has been given by Eggers.[51] Most cancers are known to be related to some form of irritation, yet there are a large number that cannot be accounted for on this basis.[51a] "Inherent predisposition" seems to play a rôle, but nothing definite is known so far as human cancer is concerned.

There may be a subtle depletion of some necessary elements in food or other factors that may be gradually undermining normal development. Wells brought up such a question when he said, "Perhaps there are changes in the incidence of cancer independent of the increased age level of the population." Otherwise there is no evidence of increase except that caused by the increased life expectancy and possibly by irritation from radioactive dust (Schneeberg and Joachimstal miners) or by influenza, which plays an uncertain rôle at present.

Occupation.—As to the occupation, there seem to be few instances in which there is any relation to cancer of the lung. Claims have been made that automobile gas, smoke, irritating dusts and tar on roads are contributing causes, but in an analysis of a large number of case histories we were unable to find a tendency in favor of any occupation, trade, profession or station of life. Laborers, office workers and housewives are most affected, but they are likewise the most numerous. Mechanics, automobile workers, painters, stokers and carpenters are involved about in proportion to their numbers. Perhaps the only instances in which the occupation may be suspected are the cases occurring in certain European mines. Incidence of cancer of the lung was shown by Arnstein[52] to be high in the workers in the Schneeberg mines, but not in the surrounding population. Schmorl[53] and others studied the problem and reported that arsenic is present in high proportions in the dust of these mines. The dust is also said to be radioactive. Pirchan and Sikl[54] showed this in a study of the pitchblende mines of Joachimstal, Bohemia, across the mountains from Schneeberg. These are medical curiosities, however, and produce no great public health problem. Other minerals, such as nickel, cobalt and bismuth have also been accused, but they do not seem to cause any effect when mined elsewhere in the world.

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51. Eggers, H. E.: Etiology of Cancer, Arch. Path. **12**:983 (July) 1931.

51a. Since this work was prepared, McNally (Am. J. Cancer **16**:1502, 1932) has shown that cigaret smoking has increased nearly forty-fold from 1905 to 1931, which increase parallels the rise in cancer of the lung. Certainly this type of irritation must not be disregarded.

52. Arnstein, A.: Ueber den sogenannten, "Schneeberger Lungenkrebs," Wien. klin. Wschnschr. **26**:748, 1913.

53. Schmorl, G.: Ueber den Schneeberger Lungenkrebs, Verhandl. d. deutsch. path. Gesellsch. **19**:192, 1923.

54. Pirchan, A., and Sikl, H.: Cancer of Lung in Miners of Jachymov, Am. J. Cancer **16**:681, 1932.

Disease.—The effect of chronic pulmonary disease often seems to be closely related to cancer of the lung. Miller and Jones [55] and Hunt [50] reported that 50 per cent of their patients gave a history of pulmonary involvement. Winternitz and his co-workers [56] and Askanazy [57] studied the after-effects of influenza and pointed out that the regeneration of the epithelium after the disease is peculiar and suggested a possible origin of cancer of the lung, although Heuper [58] could find no relation in the influenza epidemic of 1890 to an increase in cancer of the lung. Ewing [59] stated that tuberculosis is a possible factor, while others report asthma, chronic infections, bronchiectasis, syphilis and chronic pneumonia in the histories. None of the diseases reported with the possible exception of influenza yield any greater proportion of cancers of the lung than the relative incidence of the respective diseases themselves. Perhaps tuberculosis yields much fewer cancers in proportion, owing to its predominance in the young, and all the other diseases must occur during the cancer age before a cancer results. It seems that some yet unknown factors (such as the laws governing mutation) may underlie the whole problem with irritation merely initiating or hastening the process.

AGE, RACE AND SEX INCIDENCE

The age incidence of cancer of the lung is not greatly different from that of other cancers, perhaps the patients are a few years younger. In averaging the ages in 112 cases from the reports of Miller and Jones,[55] Hunt,[50] Grove and Kramer,[48] Fried,[49] Fishberg and Rubin [60] and Moise,[61] we found the result to be 49.9 years.

There do not seem to be any racial differences, although Cooper [62] stated that cancer of the lung may be more common in Jews. It seems to depend largely on the type of population. In New York City there

55. Miller, J. A., and Jones, O. R.: Primary Carcinoma of the Lung, Am. Rev. Tuberc. **21**:1, 1930.

56. Winternitz, M. C.; Smith, G. H., and McNamara, F. F.: Epithelial Proliferation Following the Intrabronchial Insufflation of Acid, J. Exper. Med. **32**:205, 1920.

57. Askanazy, R.: Ueber die Veränderungen der grossen Luftwege besonders ihre Epithel-Metaplasie bei der Influenza, Cor.-Bl. f. schweiz. Aerzte **49**:465, 1919.

58. Hueper, W.: Primary Gelatinous Cylindrical Cell Carcinoma of the Lung, Am. J. Path. **2**:81, 1926.

59. Ewing, J.: Neoplastic Diseases, ed. 2, Philadelphia, W. B. Saunders Company, 1922.

60. Fishberg, M., and Rubin, E. H.: Carcinomatous Abscess of the Lung, Am. J. M. Sc. **178**:20, 1929.

61. Moise, T. S.: Primary Carcinoma of the Lung, Arch. Int. Med. **28**:733 (Dec.) 1921.

62. Cooper, D. A.: Primary Carcinoma of the Lung, M. Clin. North America **12**:1109, 1929.

no doubt will be a high percentage of Jews, but so in England there will be more Anglo-Saxons. Our studies revealed that in American statistics the various races were represented about in proportion to their respective populations.

The incidence of cancer of the lung is higher in the male than in the female, the ratio being about 3:1. This is similar to conditions prevailing with primary cancer of the liver, Hodgkin's disease and perhaps many other malignant forms of disease. The female sex seems to have a greater predilection for cancer of the breast and the genital organs and thus contributes its quota from these specialized organs, because in the statistics of all cancers both sexes are about equally represented, as is well shown by Briese.[17]

Location.—Slightly more cancers occur in the right than in the left lung. Brunn[63] added 252 cases to Adler's[15] 374, and reported 283 cancers in the right to 246 in the left lung, 26 in both lungs, 3 of doubtful location and 68 cases in which the location was not mentioned. In the 112 aforementioned cases that we studied, there were 58 in the right lung, 50 in the left lung and 4 in both lungs. There were 24 in the right upper lobe and 17 in the left upper lobe, most of which perhaps originated from the main bronchi. There were 20 definitely in the right main bronchus region with 21 in the left, while only 14 were in the base of the right lung, with 12 in the base of the left lung. None were reported in the middle lobe.

PATHOLOGY

The pathologic process will be dwelt on only briefly because this is primarily an epidemiologic and clinical paper. Grossly, there is much difference of opinion regarding the classification, and there is little relationship between the gross and the microscopic findings. The majority of the tumors are nodular masses along the main bronchi, mostly showing at the hilus. There is a much smaller group of an infiltrating type (including the so-called alveolar type) that spreads rapidly and many times resembles lobar pneumonia in the gray state of hepatization. The miliary type frequently mentioned is not common and should, furthermore, be suspected of causing metastases until it has been proved that they are not present.

HISTOGENESIS

The time-honored classification of the histology of cancer of the lung is based on the supposed origin from bronchial epithelium, mucous glands and pulmonary alveoli. This has undoubtedly been suggested

63. Brunn, H.: Primary Carcinoma of the Lung, Arch. Surg. **12**:406 (Jan.) 1926.

by appearances of the cells in the tumor and not from any consideration of the genesis of these cells. If the cells were uniformly of one type, this grouping might not have been questioned, but many times there exist several types of cell in the same specimen, namely, columnar cells with and without mucus, all shades of undifferentiated cells and sometimes squamous or cuboidal types mixed in.

The trend of opinion seems to be veering toward the suggestion of Moise,[61] Fried [49] and others that the tumors arise from the undifferentiated cell layers of epithelium, and the end-result depends on the power remaining in these multipotential cells to differentiate. Some remain undifferentiated, others become columnar, others squamous and others mixed, depending on the individual cell and its environment during the stage of early abnormal development. MacCarty,[64] as early as 1915, pointed out the same thing with reference to all epithelial new growths.

METASTASES

Metastasis may occur early or late in the disease. Adler found it mentioned in 280 of 374 case reports. Some tumors show none, even though there may be extensive tumor formation in the lung, while a small primary tumor may localize early in distant organs. As we shall show later, distant metastasis depends largely on the growth of tumor into the pulmonary vein. The adjacent lymph nodes are first involved, with the pleura and liver in close succession. Fried has reported about 30 per cent metastasis to the central nervous system, shown clinically and verified by operation or by autopsy. Kikuth [28] also reported similar figures. Miller and Jones,[55] in a review of 808 cases, gave the following order of percentages of metastases: pleura, 35.2; lymph nodes, 30; liver, 30; lung, 21; kidneys, 15.9; bones, 10.1; suprarenal glands, 9.7; brain, 9.5; heart and pericardium, 2.7; gastro-intestinal tract, 1.1; spleen, 0.7, and muscles, 0.2. The pleural metastases are chiefly due to direct extension; metastases to the lymph nodes may be by the lymphatics or by direct extension, while the other metastases are chiefly hematogenous, from an invasion of the pulmonary vein.

COLLATERAL FINDINGS

One of the most common pathologic changes is bronchiectasis, and this is a secondary process. It is due to a closure of the bronchi by occlusion or by pressure. Commonly abscesses or cysts result in the occluded bronchi. Nearly always after occlusion there is a collapse of the tissue of the lung, and this atelectasis frequently gives the appearance of a dense lobar involvement (case 5).

64. MacCarty, W. C.: Histogenesis of Cancer of the Stomach, Am. J. M. Sc. **149**:469, 1915.

DIAGNOSIS

Clinical Considerations.—If there is to be any advance in the diagnosis and treatment of cancer of the lung, it will depend largely on a better realization of the early symptoms and physical findings. While, as Ewing has stated, there is no one factor that is pathognomonic, all taken together generally form a clear picture. This is especially true for those who have learned how to interpret the various symptoms.

With this in mind, we have departed slightly from the usual method of describing the symptomology by considering it in three classes, viz.: early, moderate and advanced. The early symptoms are the ones that need to be stressed, because they are the only ones that will lead to a diagnosis sufficiently early to save the patient's life. We cannot stress this fact too strongly. After the disease has passed the operable stage there is little difference whether the diagnosis is made one year or one month before death, except for the personal satisfaction of the physician.

Without question, the most common early symptom is the cough, with or without expectoration. It usually precedes all others by weeks or months. We prefer to consider the cough and the sputum together, because each alone is of little help, whereas together they may reveal much. If the cough is nonproductive or if it fails to respond to treatment with rest, it is important. A "brassy" or pressure cough is important, but such a cough usually comes after other symptoms (such as dyspnea) have become prominent, and it is present in any other condition when pressure exists. The same statement may be made of cornage—a tubular wheeze or blow. A persistent cough with no sputum or with a blood-tinged mucoid sputum free from tubercle bacilli affords the best early diagnostic evidence. Such sputum should be subjected to a searching study for the appearance of cancer cells, and the patient should have a careful bronchoscopic and roentgenologic study.

Although Weller [10] found sputum next in frequency to cough, its greatest importance is when it is absent in the presence of cough. As there is nothing characteristic about the sputum except that it is scant, mucoid, blood-tinged and free from the ordinary infectious agents, it seems fitting to discuss it as we have done in conjunction with cough. The "current jelly" sputum is not often found, but is of great importance. Different types of hemoptysis or of streaking of the sputum with blood are of far greater importance, especially in the absence of tubercle bacilli.

The coexistence of cancer and tuberculosis in the lungs, incidentally, offers one of the most perplexing problems in the diagnosis of conditions of the chest. The two sets of symptoms must be analyzed separately with attention to the smallest details suggestive of each

disease. If they are coincident in duration, an early separation is practically impossible.

As cough is the most frequent, so pain has the most definite significance, although it is not so common or so commonly found first. It is usually associated with moderately advanced or with far advanced symptoms. When present, it is likely to be outstanding in its character and duration. Owing chiefly to its involvement of the pleura, it may be an intense soreness, a dull, persistent ache, or an excruciating agony that even narcotics will not relieve. The last-named quality is important, because it sharply differentiates this type of pain from that in infections and pleurisy and from most other pains in the chest. Such a characteristic pain is rarely found sufficiently early to be of aid in prognosis.

The third leg of the important triad is composed of symptoms due to pressure (chiefly dyspnea), which usually mark the presence of advanced disease. They are later even than pain, but are characteristic, because few other conditions produce dyspnea or stertorous breathing so early.

In the compilation of figures on the basis of the first appearance of symptoms from the 112 case reports previously mentioned, cough was found mentioned as first (occasionally with some other symptom) 66 times; second, 11 times; third, not at all, and fourth, once. Pain was first or with some other symptom 36 times; second, 15 times; third, 4 times, and fourth, 3 times. Dyspnea was first 14 times; second, 16 times; third, 6 times, and fourth, 6 times. Frank hemorrhage appeared as a rule still later, occasionally at the terminal stage. It appeared first, however, in 5 cases; second in 9; third in 8, and fourth in 5. Blood-streaked sputum was of far greater importance. The sputum was negative in 21 cases and contained tubercle bacilli in 1. The other findings were of no particular significance, except when tumor cells were present following sloughing. As this occurred late in the disease, it is of uncertain value. Anorexia is rarely mentioned but is no doubt common. From the loss of appetite and toxemia there would be loss of weight and weakness, both of which occur late in the disease and are of limited value in diagnosis. Fever and night sweats depend on attendant infection. The absence of fever is more significant than its presence. The effects of circulatory disturbance (clubbing of fingers, cyanosis and similar symptoms) are variable and of little diagnostic value. Although pleural effusion is frequently reported, it is usually late. Its importance depends chiefly on the confusion its presence may cause in differentiating cancer of the lung from tuberculosis. Usually such effusions are tinged with blood or are bloody, especially late in the disease, but not infrequently they are serous, in which case they are difficult to distinguish from the effusions of tuberculosis.

Symptoms from metastases cause the greatest confusion of all and when detected are of little value. Their frequency in the central nervous system has been emphasized by Fried. They manifest themselves by simulating almost any type of tumor of the central nervous system. Pain in the extremities, back or neck or swelling in the neck not infrequently obscures the source of the trouble. Some of the less common symptoms are venous engorgement in the veins of the neck and chest, dysphagia, recurrent laryngeal paralysis, inequality of the pupils and hoarseness.

Physical Findings.—The physical findings do not lend themselves readily to classification because of the diversity of the gross pathologic process and the varying stages of the disease. There are some features, however, that are of great significance and help to complete the evidence of tumor. Most important is the appearance of symptoms due to a mass in the thorax such as limitation of motion, changed vocal fremitus, dulness or flatness on percussion, changed breath sounds above and below the tumor and various other signs. In the series of 112 cases from the literature that we analyzed, the physical findings, when mentioned, conformed in general to these conditions. When the pathologic process was chiefly outside the chest or when there were severe complications, the signs were confusing. It is obvious that the physical signs are not clearcut, because rarely were they emphasized or described accurately. In general, we tried to select the earliest diagnosis, which sometimes was made quite late in the course of the disease. Instead of the findings being specified, one will find in the reports "infiltrative lesions," "signs of a mass" and similar diagnoses. Dulness was mentioned 74 times; diminished breath sounds, 58 times; moist râles, 43 times; limitation of motion, 35 times; bronchial breathing, 28 times, and flatness, 16 times. There is no doubt that flatness was present many times without being mentioned. It should be present nearly always late in the disease.

There is no point to listing the many other physical findings, because they have all been mentioned a few times, depending on the pathologic process. For example, amphoric breathing was mentioned 11 times and is often present when there are excavated lesions. Hyperresonance above the mass was mentioned 9 times; distended veins in the neck, 7 times; Virchow's nodes, 4 times; other lymph nodes, 13 times, and enlarged liver, 8 times.

Roentgenologic Findings.—Perhaps no other one factor has been so important as the roentgenogram in contributing to the changed attitude toward cancer of the lung. Densities that could be coordinated with the symptoms and physical findings helped to point out primary

conditions in the lung, when without the roentgenographic evidence the diagnosis might have been something else. McMahon and Carman,[16] in 1918, expressed such a sentiment, and at that time they considered cancer of the lung to be a rare condition. They mentioned three gross types—a diffuse, a nodular and a mixed. The diffuse type shows one or more areas of increased density along the roots of the larger bronchi, homogeneous or mottled with indefinite borders extending into atelectatic tissue of the lung; the density at the hilus is not increased or may be wedge-shaped with the apex toward the hilus. The nodular type shows many varying sized nodules throughout the lung, but, as Weller has recently warned, such a type must be suspected of causing metastases until it has been proved that they are not present. Christie [65] emphasized the gradual extension of a tumor of the hilus outward with discrete blending into normal or atelectatic tissue of the lung, although there are many atypical forms. Kornblum [66] pointed out the desirability of early and frequent examination in order to follow the development. It is not always possible to do this, because many times the first picture shows complete obliteration of one whole side.

Miller and Jones have also made a worthy attempt to classify the various lesions from a combined clinical and roentgenologic point of view.

Bronchoscopy.—As the x-rays were the first important diagnostic aid, the bronchoscope is the most recent and the most definite in the information it renders. We feel that no thoracic clinic should be without a bronchoscopic service. There are two features of this service: one the direct endoscopic view, and the other the biopsy.

Jackson and his associates [67] pointed out the clear picture presented by the endoscopic view. There is a loss of elasticity of the affected bronchus, or as they described it, a fixed and "woody" tube in the case of a malignant growth. This may be present even when it is not possible to obtain a section. McCrae and his co-workers [68] described clearly the various appearances of bronchial tumors. They may be nodular, papillomatous or simply constrictive, and usually a pearly gray, but many are papillomatous, vascular and pinkish.

65. Christie, A. C.: Diagnosis of Primary Tumors of the Lung, Am. J. Roentgenol. **8**:97, 1921.

66. Kornblum, K.: Case of Primary Carcinoma of the Lung, Am. J. Roentgenol. **18**:230, 1927.

67. Jackson, C.; Tucker, G.; Clerf, L. H.; Lukens, R. M., and Moore, W. F.: Bronchoscopy as an Aid to the Thoracic Surgeon, J. A. M. A. **84**:97 (Jan. 10) 1925.

68. McCrae, T.; Funk, E. M., and Jackson, C.: Primary Carcinoma of the Bronchi, J. A. M. A. **89**:1140 (Oct. 1) 1927.

The section removed may not always be cancerous and should not be relied on entirely. If it is cancerous, there will be no difficulty in making a pathologic diagnosis. The tumor may be deep in the parenchyma of the lung, however, without extending into the bronchi.

Thoracoscopy has been used, but it adds little that may not be learned earlier and by other simpler means, unless the tumor is pleural. In that event, it may be of certain aid.

Laboratory Examination.—The diagnosis of cancer of the lung from laboratory data is disappointing outside of the study of the section. No findings are definite, except perhaps the negative ones. Sputum or pleural fluid that is negative for tubercle bacilli is important, however. The presence of malignant cells in sputum and pleural fluid is indefinite, and many times the large alveolar-like malignant cells may be overlooked. If mitotic figures are found, of course, this is more definite. Blood-tinged or bloody pleural fluid free from tubercle bacilli is very suggestive, but it is rarely found until late in the disease. In one of our cases the large alveolar type of cell was thought to be an atypical monocyte or lymphocyte.

Summary.—The diagnosis of cancer of the lung without a biopsy is difficult. It requires an interpretation of all the symptoms and findings. The history of cough, with slight blood-streaked sputum free from tubercle bacilli, gradually increasing pain of a permanent nature and increasing dyspnea form the chief diagnostic triad. Signs of increasing growth of the tumor with its symptoms of pressure, toxemia and metastases are the remaining findings.

The physical signs depend on the stage of the disease. In the early stages there are usually suppressed breathing beyond the tumor, limited motion on the side of the tumor, hyperresonance above, bronchial or harsh breathing with some scattering moist râles, and gradually increasing signs of development of the tumor, with dulness and flatness on percussion.

The roentgen picture shows the presence of a small tumor along one of the main bronchi away from the hilus, gradually spreading to involve the whole lobe or lung. A bronchoscopic view reveals a "woody" or fixed bronchus with protruding walls or grayish nodules. Biopsy of a specimen of the involved tissue shows malignant cells.

DIFFERENTIAL DIAGNOSIS

The most common and important condition to be differentiated from cancer of the lung, particularly in our work, is tuberculosis. We feel that in the past many persons with cancers of the lung have been sent to sanatoriums and have died, supposedly with tuberculosis. This was especially true before the discovery of the tubercle bacillus and the

x-rays. Lawrason Brown and his associates [69] stated that there should be only 2 per cent error in diagnosis in cases with two of the five cardinal symptoms of tuberculosis (râles in the upper third part of the chest, pleurisy with effusion, hemoptysis, parenchymatous lesion demonstrated roentgenographically and tubercle bacilli in the sputum), if such lesions are unaccounted for otherwise. Of this 2 per cent, we feel that a sizable percentage may be cancer of the lung, because the cardinal symptoms of tuberculosis may be simulated by it, even to the associated presence of tubercle bacilli. Points of greatest difference of tuberculosis are the history, age, hectic afternoon fever, characteristic roentgen picture and physical findings (râles) in the upper part of the lungs, early weakness and loss of weight and the presence of the tubercle bacilli in the sputum or pleural fluid. When cancer becomes associated with the tuberculosis, there is usually the appearance of a grave, painful, progressive disease, with characteristic roentgenographic findings added to those of tuberculosis. A cancerous pleural fluid is usually but not always hemorrhagic. Should the two diseases be simultaneous, there is no way known to us of making an early diagnosis of the cancer.

We shall merely mention other conditions that must be differentiated from cancer of the lung, leaving the details for the textbooks of medicine. Such diseases are: mediastinal tumors, malignant and benign; tuberculosis of the hilar lymph nodes; Hodgkin's disease; carcinoma of the esophagus; sarcoma of the mediastinal structures, including the thymus; aneurysm of the aorta; pneumonoconiosis (first stage); foreign body; abscess of the lung; bronchiectasis; acquired atelectasis; massive collapse; cystic lung; chronic pneumonia; echinococcus cysts; benign tumors; chronic passive congestion; substernal goiter; bronchomycosis; blastomycosis; coccidioidal granuloma, and actinomycosis.

REPORT OF CASES

Case 1.—J. P., aged 40, an Austrian waiter, gave a history of influenza at 7 years of age, and a "cold" before admission to the sanatorium, from which he never recovered. There was a cough with slight mucoid sputum, but never bloody; pain later developed along the left side of the spine, which became severe. The appetite was variable; the patient became weak, lost weight, had a slight fever, occasional night sweats and was dyspneic.

On physical examination (Dr. Ludwig), the skin was atrophic and icteric; there was bilateral limitation of motion and flatness, dulness in both upper quadrants, bronchial breathing on the right side, a few moist râles bilaterally and a friction rub between the seventh and the ninth dorsal vertebrae posteriorly, where the patient complained of pain.

69. Brown, L., and Hayes, J. N.: Pulmonary Tuberculosis, in Tice, Frederick: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1920, vol. 2, p. 361.

The roentgenogram (Dr. Barber) revealed a solid mass extending out from the left hilus, which was considered to be an abscess, with a linear density in the right lung running diagonally across the field.

Laboratory examination did not reveal any tubercle bacilli; spirochetes and fusiform bacilli were found, but malignant cells were not recognized in a hemorrhagic fluid after tapping. There was a mild secondary anemia, but all other findings were practically negative.

The patient became progressively worse and died.

Autopsy performed on Feb. 23, 1923, revealed that the essential gross pathologic process, a large, white, tough (scirrhous) tumor mass measuring about 15 cm. across, surrounded the left main bronchus below the bifurcation; the left pleural cavity was completely encased in a tumor mass ranging in thickness from 1 to 3 cm.; the rest of the lung contained a few nodules and was atelectatic. The hilar lymph nodes were enlarged and contained tumor tissue. The right lung was enveloped in a fibrous veil that was concentrated in one place to a true bony structure 1.5 cm. across running diagonally for 15 cm. There were many small tumor nodules in this lung. Metastases were present in the hilar lymph nodes, pleura, opposite lung, kidneys, suprarenal glands, gallbladder and stomach. The brain and cord were not examined.

The diagnosis was a scirrhous carcinoma of the left main bronchus of an undifferentiated cell type.

Comment.—This case represents one of the most common types of cancer of the lung—a gradually spreading mass coming off a main bronchus, extending to the pleura and metastasizing rather widely. The disease manifested itself first as a bronchial irritation with symptoms of "cold"; then as it spread pain appeared, followed by symptoms of pressure. All findings, physical, roentgenologic and laboratory, were compatible with the pathologic process. The history of influenza thirty-three years before, we feel, was of little importance. The diagnosis was made at autopsy.

Case 2.—H. K., aged 39, of Polish ancestry, born in Chicago, had been a baker, a marine and during the latter part of his life a clerk. His past history was unimportant. The onset of his condition was influenzal nine months before death, with cough, fever, variable blood-streaked sputum, followed by pain in the right side, with weakness, some night sweats, loss of weight and pleural effusion.

Physical examination (by Dr. Weissman) revealed a well developed but poorly nourished man, with a lagging in the right side of the chest, dulness of the base of the right lung anteriorly and posteriorly, bronchophony in the upper part of the right lung with fine râles, a few fine râles over the upper part of the left lung also, and diminished breath sounds over the base of the right lung.

Roentgenographic examination (by Dr. Cook) revealed fluid at the base of the right lung, with a dense process at the hilus which was thought to be a tuberculous lymph node, perhaps an old tuberculous empyema. There was no mention of a malignant condition.

Laboratory examination showed the sputum to be negative for tubercle bacilli; the effusion contained hemolytic streptococci, but no cancer cells were found. A mild secondary anemia was present (3,900,000 red blood cells), and there was leukocytosis (27,850 white blood cells). All other tests gave negative results.

Autopsy, performed on Feb. 25, 1927, revealed that the essential gross pathologic process was confined to the right lung. It weighed 2,100 Gm., including the diaphragm. The lung appeared to be covered by a fibrous layer 18 mm. thick. This layer became thicker toward the base and measured 12 mm. over the diaphragm. On cut surface, the visceral pleura on its anterior surface was 9 mm. thick. There was a cavity containing 500 cc. of sanguinopurulent fluid located in the base of the pleural cavity. In the lower lobe toward the base was a generalized saccular bronchiectasis. There was a similar condition in the upper lobe at the apex and the hilus. The upper lobe was made up of a large cystic cavity 6.5 cm. in diameter, which shaded off below into numerous similar smaller cavities. Along the left main bronchus 1.5 cm. from the bifurcation was a tumor that almost closed the bronchus and that extended downward and outward into pulmonary tissue toward the middle lobe. The left hilar glands also contained some tumor tissue. The tumor was firm, had the consistency of cartilage and measured 10 cm. at its thickest point, and almost encircled the bronchus. Out in the parenchyma there were much thickening and sloughing. No metastases were found beyond the hilar lymph nodes. The brain was not examined.

The microscope revealed a nonhyalinizing squamous cell carcinoma.

Comment.—The influenzal symptoms at the onset of the patient's illness were important, but it is a question whether they were a result or a cause. It is one mode of onset of cancer of the lung, as pointed out by Hunt. There was a marked fibrous pleuritis that may have been due to an infection, concurrent with or preceding the influenza.

There was no suggestion of a malignant growth in the diagnosis until late in the disease, when it was considered, but it was not established until autopsy.

Case 3.—L. H., aged 46, born in Germany, came to the United States at 1 year of age, and in recent years worked as helper on a brick truck. The history was essentially unimportant. The onset of the condition was a pain in the right side of the chest, followed by cough, expectoration, which was sometimes blood-streaked, weakness and loss of weight. The sputum increased and became foul-smelling.

Physical examination (by Dr. Henrichsen) revealed a flat chest, poor expansion and increased breath sounds in the upper right side with crackling râles in both lungs. The patient was too sick to be examined satisfactorily.

The roentgenograms taken on July 11, 1927, revealed erosion of the fourth and fifth dorsal vertebrae "most certainly malignant." A dense shadow was seen in the right side of the chest in which a peculiar excavation was considered to be "actimonicosis or malignancy." On July 25, the roentgenologic examination showed that beginning about the fifth interspace on the right side and following the costal grill up to and including the apex and along the right border of the spine there was an area of increased density, annular in type, with an area in the midportion that showed aerated lung tissue. This was a rather peculiar looking shadow which had the appearance of a markedly fibrotic wall as though at some time there had been fluid. It had not the characteristic appearance of a pulmonary abscess or of the usual thickened pleura. It was thought that this might represent tuberculosis, but it was held to be unusual in this type. It was stated in the report that occasionally malignant or infectious processes produce similar findings, and that endothelioma, actinomycosis or malignant growth might produce such a condition.

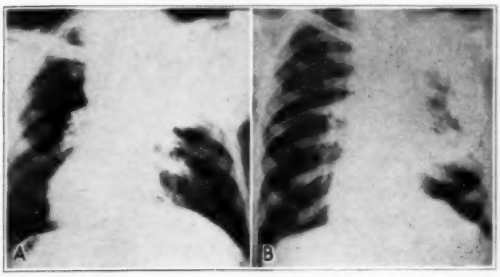

Fig. 5 (case 3).—*A*, roentgenogram taken twenty-two days before death, showing involvement of the right upper lobe by a complete consolidation resembling a massive tuberculosis ("lobite" of Bernard) or abscess. *B*, roentgenogram taken eight days before death, showing an extensive and rapidly excavated carcinomatous abscess with a thick wall.

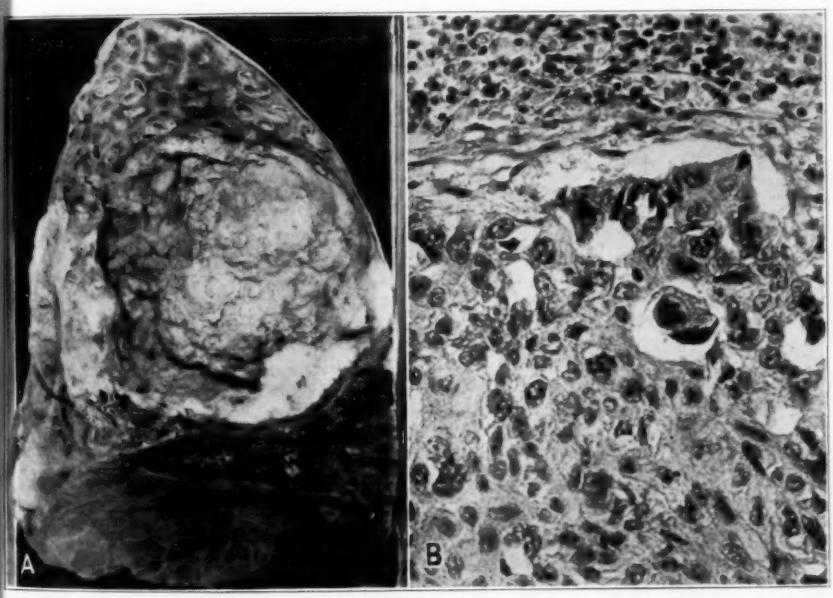

Fig. 6 (case 3).—The gross and microscopic appearance, respectively, of the right lung. Note the excavated abscess (*A*) and the nonhyalinizing squamous cancer cells (*B*). Hematoxylin and eosin stain; × 330.

The sputum was always negative for tubercle bacilli, and did not show fungi or cancer cells. There was marked secondary anemia (3,000,000 red blood cells and 10,600 white blood cells). All other tests were negative.

Autopsy, performed on Aug. 2, 1927, revealed a large carcinomatous abscess of the right lung, with a cavity measuring 3 by 4 inches (7.6 by 10.16 cm.), of a nonhyalinizing squamous cell cancer. Metastases were present in the right fifth rib, fourth dorsal vertebra, liver, left kidney, right suprarenal gland and mesenteric lymph nodes.

Comment.—This case represents the carcinomatous abscess well shown by Fishberg and Rubin.[60] It is only an advanced stage of the common massive type that has undergone necrosis and sloughing. There is no fundamental reason to class such abscesses as a separate group, but it is convenient from clinical and roentgenologic standpoints. The involvement of the spine seems to be by direct extension through the pleura, because a large tumor nodule connected the tumor of the lung with that in the spine, although there also may have been a growth into a pulmonary vein that may have accounted for it. The diagnosis was made both clinically and roentgenologically, but was not established until autopsy.

Case 4.—D. M., aged 60, an Irish-American motorman of "moderate" habits, gave a history of pulmonary involvement four years before his death that was called a "touch of pneumonia." Afterward there had been frequent colds, moderate cough, moderate expectoration, hemorrhage a year after the first attack, a dull aching pain in the left side of the chest, gradual loss of weight, moderate dyspnea, moderate weakness and marked night sweats.

Physical examination (by Dr. Rennick) revealed a lagging in the left side, dulness throughout the left lung and the upper part of the right lung, with harsh breath sounds in both lungs and suppression of breath sounds over the base of the left lung. Fluid was suspected but not found at this time, and there were no moist râles. Later, a malignant condition was suspected when the sputum continued to be negative. Still later, a positive specimen of sputum reversed the decision.

Roentgenologic examination (by Dr. Cook) revealed an erosion of the fifth dorsal vertebra which was "questionably tuberculous, and probably malignant." A haziness was noted throughout the left lung, which was dense at the base and decreased toward the apex, with a "shadow in the region of the aortic knob." There was a slight haziness in the apex of the right lung also. The condition of the lung was considered at first "undoubtedly tuberculous," but later it was considered probably tuberculous with pleurisy.

Laboratory examination showed the sputum to be continually negative for tubercle bacilli for the first three months; then one positive specimen was found. The other laboratory findings were of little consequence or were negative. There was a leukocytosis of 23,700 and 4,700,000 red blood corpuscles.

In the subsequent course the patient gradually became worse; all symptoms became exaggerated, and a paraplegia developed in the lower extremities with cystitis. The temperature rose to 101 F., and the patient died.

Autopsy, performed on Feb. 21, 1928, revealed that the essential pathologic process was confined to the lungs. The right lung contained a small tuberculous

cavity with several healed tubercles in the upper lobe. The left lung was quite dense throughout. Cut sections through the bronchi and lung showed a tumor mass in the left bronchial wall. This mass extended for a distance of 6 cm., infiltrating the surrounding lung tissues for varying distances, and extended posteriorly to infiltrate into the visceral pleura. There was a marked bronchiectasis in the lung below the tumor and a considerable amount of caseation throughout the tumor mass which may have been tuberculous. The infiltration was not so dense as usual. The color was a gray black, and the growth was spongy.

At the fifth dorsal vertebra there was a tumor mass connecting with the pleura that extended into the interspace between the fourth and fifth dorsal vertebrae, eroding and infiltrating through the centrum of the fifth vertebra and the intercartilaginous disk. This mass extended to the edge of the spinal canal but not into it.

There were no metastases other than those mentioned. The type of cell is "oat cell" or squamous cell type.

Comment.—This is one of four cases of cancer of the lung associated with some form of tuberculosis. It is difficult to make a diagnosis of such a combination. The only means available are to look for the appearance of characteristic shadows of cancer on the roentgenogram and to confirm it with the bronchoscope. In the onset of cancer of the lung associated with a moderately advanced tuberculosis the patient rather suddenly begins to show the symptoms of a grave, unrelenting process that is not like the fluctuating course of tuberculosis, but directly downward without any sign of remission. It was also the second case in succession with metastasis to the spinal cord, which caused the symptoms that led to a definite diagnosis. Here again it may have resulted from a penetration of a pulmonary vein, although this was not demonstrated. The diagnosis was in doubt clinically, but when the metastases appeared in the spine the roentgenogram was definite.

Case 5.—J. J., aged 44, a Polish-American tailor, smoked heavily and drank moderately, but otherwise his history was unimportant. His illness was of influenzal onset twenty months before death, followed by severe pains in the chest, and was diagnosed as heart disease. There was a slight cough and loss of weight. Nine months before death an intense pain developed on the right side of the chest. Hemoptysis and expectoration then occurred, and later night sweats appeared.

Physical examination by Dr. Rosenbloom revealed a sallow-skinned white man with a phthisical habitus. Lagging was present in the right side, impaired resonance in the upper part of the right lung, harsh breath sounds and a few fine râles at the apex. A malignant condition was suspected. Later, the right side of the chest and neck became swollen, and the veins became engorged. All reflexes and sensations below the sixth dorsal vertebra gradually disappeared.

Roentgenologic examination by Dr. Cook revealed the entire field of the upper part of the right lung to be hazy and dense, with a compression of the bronchus, "probably pneumonic—primarily tuberculous." No pathologic process was found in the dorsal vertebra around which a compression myelitis originated.

Examination of the sputum was always negative for tubercle bacilli. All other laboratory tests were negative except that at times a mild leukocytosis was shown. Bronchoscopic smear from the right bronchus did not reveal any tumor cells. After compression of the cord, laminectomy was performed (by Dr. Thomas) with removal of a tumor, which proved to be metastatic carcinoma.

Autopsy performed on Sept. 16, 1929, showed the following pathologic changes: The bronchus leading to the right upper lobe was obstructed by a soft gray mass measuring about 10 cm. in diameter. Below this, the mass spread out in all directions into the right upper lobe. Distal to this, the bronchi were distended and filled with greenish-yellow pus which accumulated in small and large cavities with thin necrotic walls. The bronchi stood out prominently and caused a marked infiltration about them.

The glands in the right tracheobronchial region and all the posterior mediastinal glands were composed of soft white tissue in which there were smaller yellowish areas.

The trachea and the right bronchus contained small nodular elevations composed of the same soft white material.

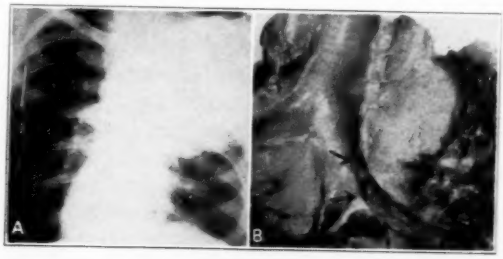

Fig. 7 (case 5).—*A* roentgenogram of a right upper lobe showing massive involvement (similar to case 3 but without excavation). *B*, photograph of gross specimen, showing bronchial tumor in eparterial bronchus and a huge mass above, causing compression atelectasis of the pulmonary tissue.

From the level of the fourth to the ninth dorsal vertebra there was a soft, spongy purulent mass occupying the spinal canal. Above this the spinal cord and the dura appeared intact. Below it the spinal cord was soft and the dura slightly discolored. Over the dura in this region and at the place where the lamina had been removed in a previous operation, there were masses of firm yellowish-white tissue resembling the mass in the lung. The spinal column in this region was made up of softened and necrotic bone, pressure on which allowed the escape of reddish-brown purulent material.

Metastases were found in the mediastinal lymph nodes, vertebrae, spinal cord and peripancreatic lymph nodes. The involvement of the cord caused a compression myelitis.

Comment.—This case is much like case 1, except that the involvement was in the right upper lobe and there was a metastasis to the spine, apparently by the blood stream. It was the third in succession involving the spinal cord. The cell resembled an "oat cell," but such a designation

has no significance, because there are all shades of differences in the undifferentiated cell. The diagnosis was made by laminectomy, and not by any pulmonary signs or symptoms. Even the bronchoscopic examination failed to yield definite evidence. There was a tumor mass in a smaller pulmonary vein extending into the upper lobe.

Another important feature of this case was that by roentgenographic and physical signs the right upper lobe appeared to be completely consolidated, while the gross pathologic process revealed a tumor of the hilus extending outward about half way to the pleura with only collapsed lung in the remaining portion.

Case 6.—A. W., aged 50, an American barber, with no history of cancer, but a history of both gonorrhea and syphilis, was treated for syphilis two years

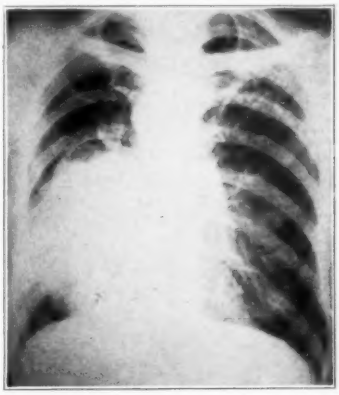

Fig. 8 (case 6).—Roentgenogram in case 6, taken seventeen days before death, showing a mass coming out from the hilus of the left lung.

before admission to the hospital. The Wassermann reaction had been positive, however, for twenty years. Seven years before admission he had a resection for gastric ulcer. The onset of his illness was with a "cold" in 1921, which developed into a typical tuberculosis. The patient entered the Cook County Hospital, where the sputum was found to be positive for tubercle bacilli. There was no fever or night sweats. His complaints on entering the sanatorium were of cough, expectoration, weakness, loss of weight and nocturia, all of which seemed to indicate a tuberculous process on an old syphilitic infection.

Physical examination by Dr. Weissman revealed the following abnormalities: The chest was emphysematous with retraction above and below the clavicles. There was impaired resonance on the right side and over the left base. The diagnosis was tuberculosis with possibility of carcinoma.

Bronchoscopy was suggested but was never done.

A roentgenologic examination by Dr. Cook revealed slight haziness in the upper part of the right lung and "several annular shadows on the root of the left lung which had the density of a glandular structure commonly seen in

lymphatic lymphoma." Four months later Dr. Cook reported that the root of this lung revealed a "well defined haziness with the appearance of a pneumonic process." He suggested that a malignant condition be considered. The right upper lobe showed "evidence of an old tuberculosis."

The laboratory examination revealed one specimen of sputum positive for tuberculosis, also 4 plus Wassermann and Kahn reactions and 39 mg. of nonprotein nitrogen per hundred cubic centimeters of blood. Otherwise, the examination gave essentially negative results.

The subsequent course showed that during the last six months of life when the mass was developing in the region of the root of the left lung, the patient's

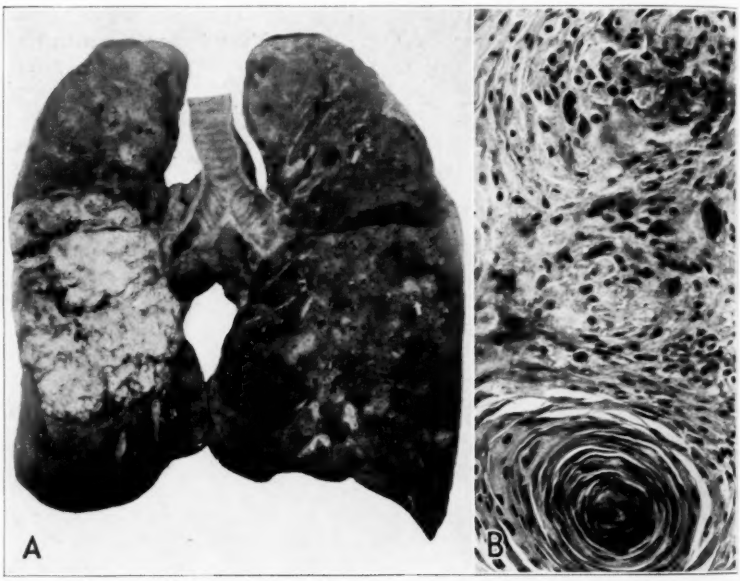

Fig. 9 (case 6).—*A*, photograph of gross specimen. *B*, photomicrograph showing a hyalinizing squamous cell cancer with epithelial pearls. No metastases were found anywhere. Hematoxylin and eosin stain; × 330.

course was definitely and progressively downward. Clinically, it was obvious that a chronic, rather mild, fibroid tuberculosis on an old syphilitic infection had abruptly changed to a grave condition that became worse without remissions.

Autopsy was performed on July 12, 1931. In the midportion of the lower lobe of the left lung was a large caseous mass about 15 cm. across, rather sharply demarcated from the rest of the pulmonary tissue, with some sloughing in the central portion. There were old healed tuberculous nodules in both upper lobes, especially the right, and an acute pneumonic infiltration in the upper left and lower right lobes.

On the convex surface of the upper portions of the temporal and parietal lobes of the brain there was an accumulation of considerable clear yellowish fluid. No

tubercles were found here or at the base of the brain. There was no accumulation of fluid at the base, and no tumors were present on section.

The microscopic diagnosis was a typical squamous cell cancer.

Comment.—This case is similar to case 4 in that a cancer developed on a tuberculous infection. It is different in that no sign of metastasis was found anywhere. The tumor mass contained large numbers of tubercle bacilli; so many that after an acid-fast stain of a smear of the tissue the process was called caseous pneumonia. There was great surprise when the section was examined. Here was an example of a relatively easy clinical and roentgenologic diagnosis, with a confusion of the gross pathologic lesions.

CASE 7.—S. L., a Polish-American housewife, aged about 47, presented an uneventful early history. The onset of her condition was pleuritic pain in the lower right part of the chest ten months before death, fever, night sweats, cough expectoration, weakness, anorexia, insomnia, headaches and loss of weight. She went to the Cook County Tuberculosis Hospital for six months, where some improvement was noted, but this soon disappeared and she was readmitted with exaggerated symptoms and a marked dyspnea. This time she was sent to the sanatorium.

Physical examination by Dr. Fremmel revealed a malnourished woman with dyspnea and cyanosis, a lagging in the right side and increased tactile fremitus on the right. There was marked mental dulness. There was dulness over the upper part of the left lung with flatness over the whole right lung. Râles were heard on the right with amphoric breathing in the upper part and whispered pectoriloquy. On the left there were a few râles.

A roentgenogram revealed a dense shadow over the whole right lung, with a moderately dense shadow out from the left hilus, which was considered characteristic of tuberculous empyema. There was a resemblance to a malignant condition, but from the history it was considered more probably tuberculosis.

The important features of the laboratory examination were 4 plus positive Wassermann and Kahn reactions, sputum negative for tubercle bacilli, a profound leukocytosis (31,200 white blood cells) and an increased red cell count and hemoglobin (5,570,000 red blood cells and 95 per cent hemoglobin). An examination of a small quantity of a bloody pleural fluid revealed a "few monocytes and many varying sizes of lymphocytes." Some of the latter cells may have been tumor cells. A bronchoscopic examination was recommended, but it was not done.

Autopsy was performed on Sept. 6, 1931. The whole right lung consisted of a consolidated mass resembling caseous pneumonia. The upper lobe contained coal pigment and a slight amount of fibrosis. There was a metastatic focus in the midportion of the left lung resembling tuberculous bronchopneumonia. There were also discrete nodules toward the base and apex resembling foci of tuberculosis, with the difference that they had a circular rather than nodose appearance. The hilar lymph nodes contained some type of metastatic material. There were metastases only in the tracheal lymph nodes. The brain was not removed, by special request, although there were symptoms of a tumor of the brain.

The cytologic diagnosis was an "alveolar cell" cancer.

Comment.—This case presents the classic picture of so-called alveolar carcinoma of the lung. The gross pathologic process resembled the

gray stage of lobar pneumonia. The cells resembled normal alveolar cells, and without close observation might have been mistaken for large lymphocytes. That is what happened in the examination of the fluid from the pleura. No mitotic figures were found even on section. The patient's course was typical of tuberculosis, except that tubercle bacilli were never found and there was never a typical tuberculous empyema.

CASE 8.—J. R., aged 50, a Bohemian butcher, was from the private practice of one of us (A. J. H.). The patient's mother died of tuberculosis when the patient was 12 years old. His history was otherwise unimportant. The onset of his condition was with a cold and a cough nine months before death; then followed pleurisy with effusion seven months before death; severe cough with hemorrhage; the presence of blood varying from streaks to clots five months before death;

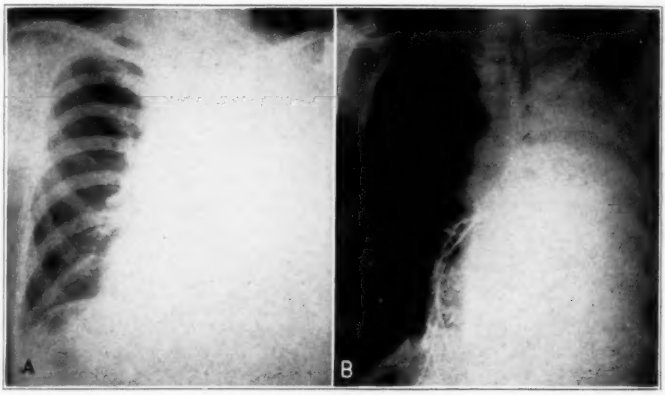

Fig. 10 (case 8).—Roentgenograms showing in *A* obliteration of all markings on the right and in *B* the stoppage of iodized oil in the right main bronchus.

gradually increasing dyspnea; epigastric pain; loss of weight; night sweats, and weakness. The patient was admitted to the sanatorium for complete study.

Physical examination by Dr. Collins showed the following signs and symptoms: There was no movement of the right side. The veins of the neck were dilated. Flatness existed over the right lung, and the left was normal. Bronchial breathing was heard over the upper anterior and posterior portion of the right lung; no râles were heard, but there were diminished breath sounds at the base of the right lung. The liver was enlarged. The diagnosis was "carcinoma or tuberculous empyema."

The roentgenogram revealed an opaque right side from the apex to the base. The left side was clear, probably owing to an empyema. After an injection of iodized oil, the right bronchus showed a complete stricture about 8 cm. from the bifurcation. Oblique and heavily exposed films revealed a few calcified lymph nodes near the hilus, but no other difference.

Paracentesis revealed a scant bloody fluid that clotted and was negative for tubercle bacilli and tumor cells.

Bronchoscopy revealed a mass in the right bronchus, obliterating the bifurcation, and granulated masses in the trachea, from which a specimen was taken that was found to be malignant.

Laboratory examination showed the pleural fluid and sputum to be always negative for tubercle bacilli. No cancer cells were found in the bloody effusion obtained by tapping the pleural cavity late in the course of the disease. An amyloid test was done, and 33 per cent of dye was removed in one hour. A biopsy specimen disclosed a medullary carcinoma of the small round undifferentiated cell type.

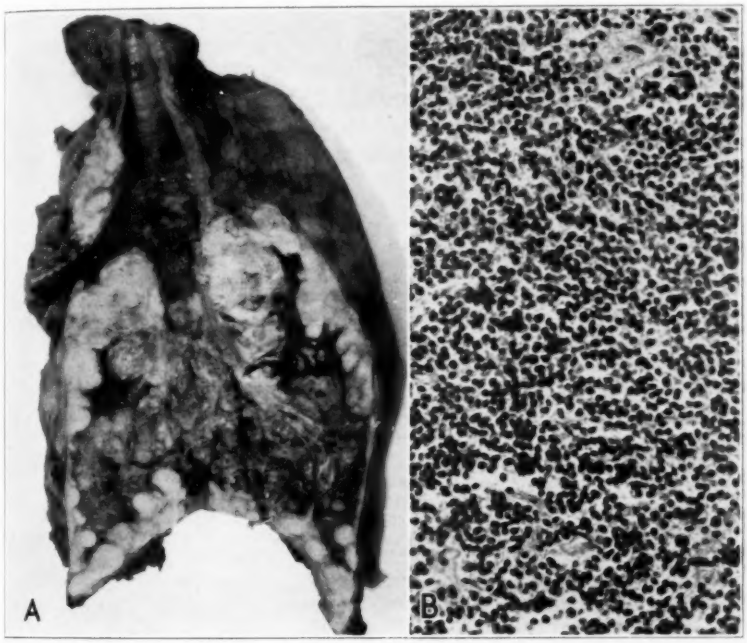

Fig. 11 (case 8).—*A*, photograph of the gross specimen. Note the bronchiectasis toward the base. *B*, photomicrograph showing a homogeneous type of undifferentiated small round cell. Hematoxylin and eosin stain; × 330.

In the subsequent course the patient failed rapidly, breathing became stertorous, and death occurred only a few days after the bronchoscopy.

An autopsy was performed on Feb. 21, 1932. The right lung was solidified in its lower two thirds. The upper third was boggy and atelectatic. When the trachea and bronchi were opened the mucosae were found to be hemorrhagic. The right main bronchus showed nodules 2 cm. from the bifurcation. Farther down these increased, giving a corrugated effect. At the first division toward the origin of the bronchus of the upper lobe and extending radially to include the parenchyma of the lung, pleura and bronchial lymph glands was an irregular grayish-pink necrotic tumor mass. Many bronchi were seen to be dilated and to exude

mucopus from the cavities thus formed. The pleura was extensively infiltrated by a coat of tumor tissue from 2 to 3 cm. in depth. The bronchial lymph nodes reached a diameter of 8 cm. and contained a calcified focus and also what appeared to be a caseous tuberculous focus. The left lung was pinkish-gray-black. One fibrous adhesion extended to the thoracic wall from the apex, which contained a few small palpable nodules. There were metastases to the right pulmonary pleura, pericardium, bronchial periaortic and peripancreatic lymph nodes and liver.

Comment.—This patient presented early symptoms of tuberculosis, including a typical-appearing pleural fluid. The distinguishing feature was that no tubercle bacilli were ever found, although the effusions obtained in the first few tappings were not examined, and many caseous and calcified lesions were present, indicating a very old and healed infection. Later, by injection of iodized oil and bronchoscopic section, the correct diagnosis was easily made. The one predominant cell was sarcomatous in appearance and perhaps would have been called that by the older pathologists. The metaplasia into the bronchial types of cell and structure, however, showed the true character.

CASE 9.—M. Z., aged 20, an Austrian office girl, who came to the United States two years before her death, did office work and then worked at a machine. At 4 years of age she had a gland removed from her neck; at 8 years of age she had diphtheria; at 14 and again at 16 she had influenza. After the first attack she was treated with tuberculin for a residual pain in her left side. After the second attack she noted an occasional fever. At 18 years of age she felt well again, but what was called appendicitis soon developed, for which an operation was performed. Pains developed in her chest after the operation, and she spit up a little blood. Ever since that time she had expectorated occasional blood-streaked sputum, but had no cough.

Physical findings by Dr. Caroline McDonald revealed a well nourished young woman apparently in good health, with a slight lagging on the right side, slightly impaired resonance in the upper part of the right lung, with more impairment posteriorly at the angle of the scapula, and a few râles. There was a large cystic mass in the region of the right ovary. The diagnosis was moderately advanced "A" tuberculosis, with a cyst in the ovary. Later there appeared a gradual consolidation of the whole right lung with nodules developing in the axilla and the cervical region. The right pupil became dilated also.

Roentgenologic examination showed a small tumor mass along the right main bronchus about 2 cm. in diameter, which was perhaps a lymph node. A later picture revealed a density of the whole right side, considered to be tuberculous empyema, abscess and tumor, at different times.

Laboratory examinations revealed the sputum to be persistently negative for tubercle bacilli, and the Wassermann reaction to be 2 plus, with other reactions practically normal. A biopsy of a subcutaneous nodule revealed carcinoma by frozen section.

Autopsy was performed on Aug. 29, 1924. The essential gross pathologic process was: a tumor mass in the right lower lobe about 7 cm. from the bifurcation. The mass was firmer than the surrounding tissue of the lung, which was collapsed, brownish, and contained scattering discrete nodules beneath the pleura and in the parenchyma. The hilar lymph nodes were enlarged into huge masses,

and they appeared to extend into the bronchus near the hilus in papillomatous masses. Metastases were found widely disseminated throughout the body as follows: large masses from 5 to 8 cm. in diameter in the liver, tracheobronchial lymph nodes, right and left pleura, kidneys, mesentery, pancreas, fundus of the uterus, glands of the hilus of the spleen, diaphragm, peritoneum, ovary and broad ligament, thyroid gland, right breast, Virchow's node (right) and gallbladder. The brain and cord were not removed. The right parovarium revealed a large sacculated tumor mass about the size of the fist, containing a large amount of serosanguineous fluid. There were accessory cysts along the tube and in the broad ligament. There were a few grapelike tumor masses around the left ovary and in the left broad ligament.

Comment.—The reasons for not considering the condition primary in the lung are: 1. There was a definite cancerous cyst of the ovary—a more common type of tumor in the female. 2. The cell type was the same as that found elsewhere. 3. The growth in the lung resembled primary cancer grossly but not microscopically. The cancer nodule pushed through the bronchus and elevated a normal bronchial mucosa with normal mucous glands. Cytologically, there was no pulmonary tissue that appeared cancerous.

It is possible that there was a double primary process, but it is difficult to prove and seemingly improbable.

Case 10.—Mrs. G. N., an American housewife, aged about 44, was referred to Dr. Henrichsen by Dr. Brandle for diagnosis. No family history was obtained. The complaint was a cough for several months, without expectoration or blood. There was no loss of weight, and she felt well generally. She smoked heavily.

Physical findings by Dr. Henrichsen revealed increased breath sounds over the left anterior part of the chest, almost bronchial in character, with râles from the hilus up and outward on the left. With the history of cough and the tumor shown in the roentgenogram, a malignant condition was suspected, and the patient returned to Dr. Brandle.

A roentgenogram revealed a dense mass along the medial border of the left hilus that did not extend far into the pulmonary tissue. It resembled a mediastinal tumor.

The patient was operated on for an ovarian cyst, but did not recover from the operation.

Autopsy revealed a tumor mass completely enveloping the left main bronchus and measuring about 8 cm. across. The tumor mass had penetrated the main bronchus and had completely occluded it.

The cytologic diagnosis was an undifferentiated basal cell type of carcinoma.

Comment.—Owing to the operation for ovarian cyst, there is some doubt about the origin of the tumor in the lungs. The cell type, however, is characteristic of neoplastic pulmonary tissue. Without this definite proof, however, there could be no positive diagnosis of the origin. The history of being a heavy smoker may be of significance.

Case 11.—G. I., aged 63, an American, with an uneventful early history, worked for forty-one years in a department store. Four years before his death an advanced

tuberculosis developed with cavities in both upper lobes. Eighteen months before death the patient had a nodule removed from the neck that proved to be a metastatic carcinoma.

According to the first roentgenologic report on the chest by Dr. Cook on May 14, 1929, the condition was "typical of well advanced tuberculosis." On Sept. 26, 1930, a fluid was noted on the left side. On Jan. 9, 1931, a phrenic exeresis was performed on the left side "with no frank evidence of metastatic malignancy," but on June 22, 1932, there were two well marked areas near the periphery that were "seen in metastatic conditions" and the right lung root showed "an active process which is probably of the same character."

The laboratory findings other than the biopsy revealed only a gradually progressing anemia and sputum negative for tubercle bacilli after March 21, 1930. Practically every common laboratory examination was performed, however.

Fig. 12 (case 11).—A photograph of a cross-section of the gross specimen, showing the tumor masses represented in the following roentgenograms. Note the primary tumor at the arrow and the point from which the section was taken.

Autopsy, performed on Sept. 4, 1932, revealed the following pertinent pathologic changes: A tumor crater was found in the right main bronchus measuring 2 cm. across and raised about 3 mm. above the surface of the mucosa. The base extended almost around the bronchus and up and down the bronchus for a distance of from 1 to 1.5 cm. After section, the tumor was found to penetrate through the wall of the bronchus as a solid white mass and extend outward into the tissue of the lung, involving lymph nodes, vessels and pulmonary structures for a distance of from 3 to 5 cm. The right pulmonary vein was penetrated by a fungating mass about 7 mm. across that proved to be tumor tissue, and was no doubt the source of the early metastases. There were two large grayish-white tumor masses in the bases of each upper lobe measuring about 10 cm. across, two in the apexes of each lower lobe measuring from 6 to 8 cm. in diameter, and several smaller ones in the apexes, middle lobe and bases of both lungs. The blood revealed the presence of tumor cells and mitotic figures. The hilar lymph nodes were markedly involved, as were the liver and the left submaxillary region including the skin.

The brain was not examined; however, there were no symptoms of involvement of the central nervous system (figs. 12, 13 and 14).

CASE 12.—J. D., aged 47, a German machinist, was a moderate user of alcohol and tobacco. He complained of cough that had been noted for four months, expectoration that had been present for one month, a transient pleuritic pain, dyspnea, fatigue, loss of weight and headaches. There had been one specimen of sputum positive for tubercle bacilli at the dispensary.

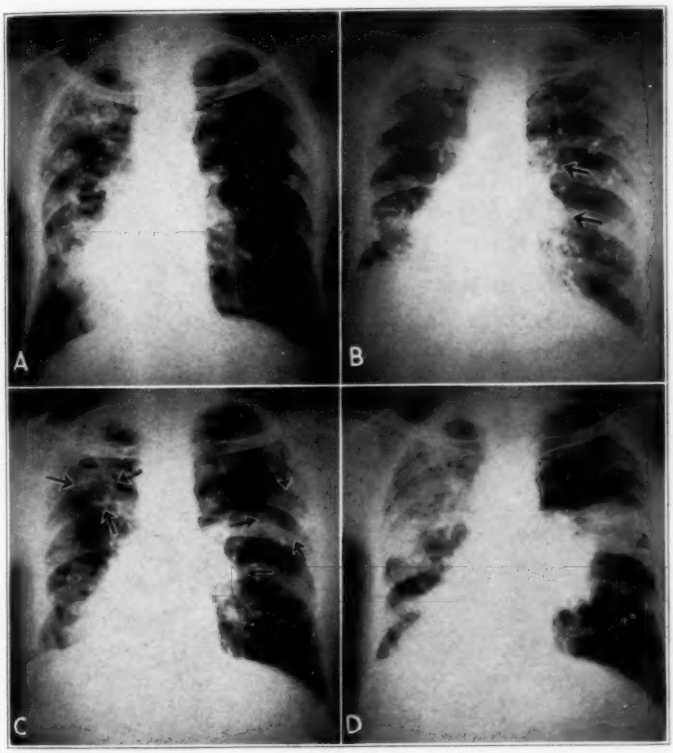

Fig. 13 (case 11).—*A*, roentgenogram taken thirty-nine months before death showing extensive tuberculosis more marked in the left lung. *B*, roentgenogram taken nineteen months before death showing marked healing of the tuberculosis with a suspicious thickening of the right main bronchus out from the hilus. *C*, roentgenogram taken eleven months before death showing an exaggeration of a tumor at the hilus with a large round mass appearing in the left upper lobe and a smaller one in the right lower. *D*, roentgenogram taken three months before death, showing an exaggeration of all the markings.

Physical examination by Dr. Davison revealed an impairment of motion and resonance at the apexes of both lungs, more on the right; flatness and absence of

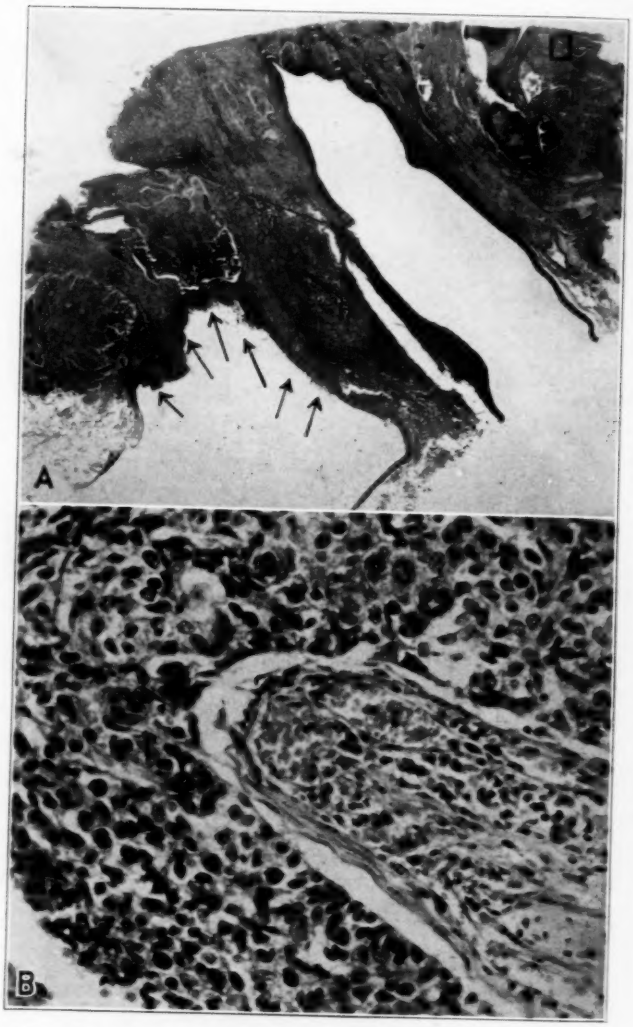

Fig. 14.—*A*, a conjoint photomicrograph of the bronchus (upper right corner) and the great vessels (lower). The primary tumor began in the bronchus (upper right) and extended around the pulmonary artery in the middle and into the pulmonary veins marked by the arrows. Hematoxylin and eosin stain; × 6.6. *B*, an undifferentiated ("oat cell") type of nonhyalinizing squamous cell cancer, represented in small square in *A*. Hematoxylin and eosin stain; × 330.

breath sounds at the base of the right lung; a few râles in the apex of the right lung. A malignant condition was suspected.

Roentgenologic examination by Dr. Cook showed that the findings were compatible with advanced pulmonary tuberculosis. Bronchoscopic examination revealed obstructions about 1.5 cm. from the bifurcation on the right but no tumor. A section of prepared pleural fluid revealed carcinoma cells. One examination for tubercle bacilli gave doubtful positive results. All other tests were essentially negative.

Autopsy, performed on Oct. 1, 1932, revealed a sclerous type of mesothelioma (endothelioma) of the right pleura, extending into the right lung, with other metastases to the liver and the left kidney. The brain was not examined, although the headaches were suggestive of metastases.

Comment.—A careful recheck of this specimen revealed a cancer of the small lower bronchi. Sometimes the differentiation of a so-called "edothelioma" from cancer of the lung is difficult.

Case 13.—A. A., aged 52, a Pole, worked three years as a coal miner and then as a metal worker. Other factors were uneventful. The onset of his condition began with cough, expectoration and fatigue, eleven months before death. Subsequent symptoms were loss of weight, fever, night sweats, dyspnea and numbness in the left leg.

Physical examination by Dr. Davison revealed the base of the left lung retracted posteriorly; fremitus increased in the apexes but decreased in the base of the left lung; resonance decreased in the apexes and base of the left lung but increased elsewhere, and absence of breath sounds in the base of the left lung. The diagnosis was deferred. The roentgenologic examination at first was suggestive of a malignant growth. Iodized oil failed to reveal anything definite. There appeared to be metastatic tumors in the leg and the skull. A nodule from beneath the skin revealed a metastatic carcinoma. A pathologic fracture of the left leg occurred two months before death. Bronchoscopy was not completed because of noncooperation of the patient.

Autopsy was performed on Dec. 18, 1932, and revealed the following important pathologic changes: The lungs were markedly anthracotic as well as the pulmonary and hilar lymph nodes. The right apex contained an old fibroid tuberculous lesion with calcification. There was a fungating tumor at the base of the left main bronchus centering 5 cm. below the bifurcation and extending upward to the bifurcation and downward for another 5 cm. and into all adjacent bronchi. There was extreme bronchiectasis with numerous bronchiectatic abscesses. The tumor had grown forward and enveloped the great pulmonary vessels, completely occluding the upper main pulmonary vein and growing into it toward the heart and into the auricle in the form of a pendulous mass. There were numerous bronchiectatic cavities in the anterior part of both lobes, most of which contained encysted mucus. Microscopic examination revealed an undifferentiated basal cell carcinoma.

Comment.—The important feature here is the same as in case 11, the origin of the metastases by extension into the pulmonary vein. It appears that this may be the chief explanation of widespread metastases of cancers of the lung (fig. 15). This condition will no doubt be found more often if it is looked for.

GENERAL ANALYSIS

In the analysis, only 12 of the 13 cases are considered because one was most likely metastatic and only simulated a primary carcinoma. It was included, however, because it resembled a primary carcinoma so closely.

The average age of the patients in this group of cases was 49.4 years for the males, 45.5 years for the females, and 48.7 years for both sexes; i. e., the incidence of cancer of the lung is chiefly in the fifth and sixth decades of life. There were 10 males and 2 females—a ratio

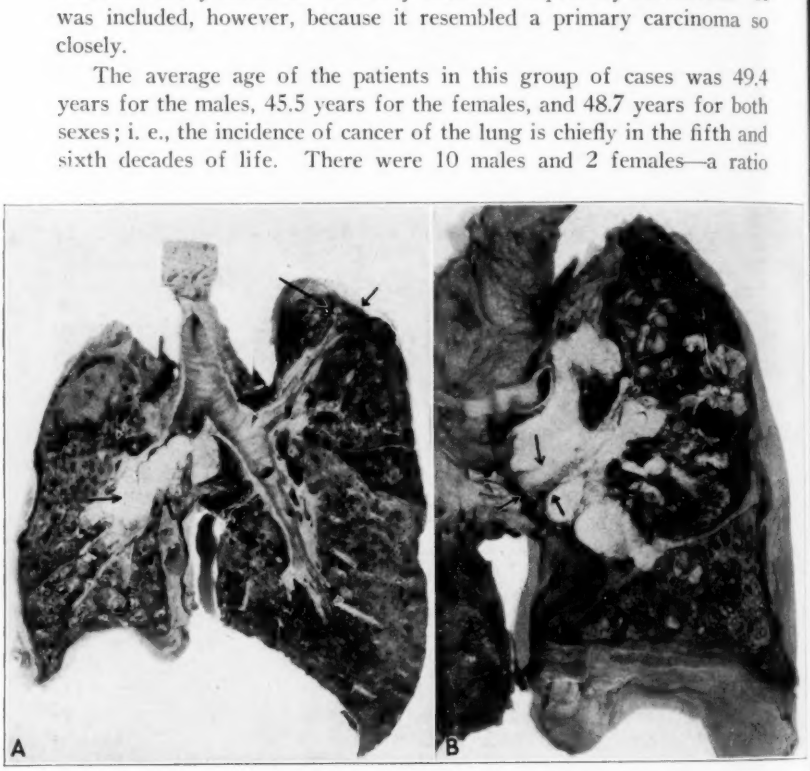

Fig. 15 (case 13).—Photographs of lung sections. *A*, posterior view showing the tumor in the left main bronchus and an apical fibroid tuberculous lesion in the right, found only at autopsy. *B*, anterior view showing a pendulous tumor growth extending into the left auricle from the left pulmonary vein.

of 5:1. The racial incidence is about what could be expected, that is, in proportion to the numbers of the various races represented. There were 3 Teutonic, 5 Slavic, 1 Celtic and 3 American patients. No history of carcinoma was obtained from any patient. The occupational incidence was of the same degree and significance as the racial incidence. There were 1 clerk, 2 housewives, 6 inside laborers (1 waiter, 1 mechanic, 1 baker, 1 barber, 1 tailor and 1 butcher) and 3 outside laborers (1 brick truckman, 1 coal miner and 1 motorman). Of disease inci-

dence, it is noteworthy that 4 patients gave a history of influenza; in 2 patients, this immediately preceded the onset if it was not actually the onset, simulating influenza. In several of Hunt's cases the condition began with influenza. One patient's condition began with a "cold"; another patient gave the history of a chronic bronchitis; 1 had healed minimal tuberculosis; 2 had chronic moderately advanced tuberculosis, and 1 had healing advanced tuberculosis. One positive finding was doubtful. Two patients had 4 plus Wassermann reactions, and 3 gave histories of excessive smoking. One patient (case 6) had a 4 plus Wassermann reaction and tuberculosis.

The appearance of symptoms may be summarized much as in previous paragraphs. Cough led the list (first, 8 times; second, once); pain came next, appearing first in 2 cases, second in 4 and third in 1; the other symptoms appeared later, the most important of which was dyspnea. In 1 case the first symptoms were not detected because of tuberculosis; in another, because of influenza. Tubercle bacilli were found in 5 cases. In 1 case the presence of bacilli confused the issue and caused a correct clinical diagnosis to be reversed, and in another a tuberculous lesion was discovered only at autopsy. In the other cases the finding of tubercle bacilli made little difference. One patient with a 4 plus Wassermann reaction gave a history of an old syphilitic infection, but another patient (a woman) with this reaction gave no history of syphilis.

In the physical findings, the presence of lagging and of limitation of motion were sufficiently important to cause the examiner to lay special emphasis on them. They were recorded four and five times, respectively. A flat chest was emphasized in 3 cases. Distended veins in the neck (a late sign) were present in 2 cases. The most important physical signs were those of tumor, impaired resonance, dulness and flatness over the tumor and hyperresonance above. Impaired resonance is not so important, because it may be present in any pathologic process in the lung; flatness is not so important either, because it nearly always appears late in the disease, and when it does, the diagnosis is obvious. A sharply outlined area of dulness, however, is set apart rather early as something unusual. This is particularly true in the lower two thirds of the chest. In 7 of the patients, dulness was found rather early. The signs of obstruction were manifested by diminished breathing beyond the tumor, with rough or bronchial breathing in the region of the tumor. Râles were usually few and of a moist type. Occasionally they were absent until late in the disease. The symptoms and findings of metastases were variable, depending on the location. In the spine there was frequently a compression myelitis, and in the brain, signs of brain tumor.

The diagnosis was made by autopsy in all 12 cases. Clinically, a definite diagnosis was made in 5 cases, a presumptive diagnosis in 5 and an incorrect diagnosis in 2. Roentgenologically, definite evidence was found in 6 cases (in 2, only by the spinal metastases), presumptive evidence in 3 and negative evidence in 3. Bronchoscopy and biopsy established the diagnosis in 2 cases, but gave negative results in 1, while biopsy of a metastatic growth established the diagnosis in 3. In 1 of these (case 11) the first sign of cancer was from a metastatic growth in the submaxillary region. The advanced tuberculosis confused both symptoms and physical findings until the pulmonary metastases appeared in the roentgenograms. The laboratory examinations (exclusive of the study of sections) did not contribute any positive information that was of help in diagnosis, except in case 12 in which the diagnosis of a malignant growth was made on the basis of the sectioned sediment of the pleural fluid. With our present information and equipment, there is only 1 of the cases in which there would be any excuse for missing the diagnosis either clinically or roentgenologically, and in all but 2 or 3 the diagnosis should have been made by bronchoscopy and biopsy. The "alveolar" type (case 7) was similar to tuberculosis, especially early. Three of the patients with sputum positive for tubercle bacilli presented other symptoms so characteristic of cancer that there should have been little difficulty in discounting the tuberculous findings.

We feel that laboratory examination can aid a great deal more than it has in the past. The sputum and fluids of any kind should be centrifugated, the sediment hardened in formaldehyde, sectioned, stained, and the sections studied carefully. In 1 patient (case 7, the "alveolar" type) numerous cells were found in the pleural fluid and sputum, but there were no mitotic figures; furthermore, the cells resembled large lymphocytes so closely that they were thought to be modified lymphocytes. Since this report was finished, a definite diagnosis has been made in 2 cases by means of sectioned sputum before any other method was employed.

COMMENT

Since a tremendous and unquestionable increase in cancer of the lung has been revealed by a study of the records of autopsies, it is pertinent to attempt to analyze the causes. While disease, smoke, dust and modes of living may have been the cause of some of the increase, we feel that better diagnosis and changed conditions have contributed the most.

Significant features from the statistical figures are that at the beginning of each report the incidence is nearly always low, irrespective of the time, which may be 1900 with some authors or 1915 with others.

Following the World War all figures rise rather sharply till many exceed 2 per cent of all autopsies, reaching the peak about 1928. This again raises the question of whether all the patients with cancers of the lung were found or whether those who came into the clinics may not have been a sporadic selection. At least this must be considered, because Lubarsch's [70] figures for 1920 revealed an incidence at autopsies of only 5 per cent for all Germany. Karsner [71] estimated the incidence at autopsies for America at 0.7 per cent. With over 95 per cent of bodies not examined, it behooves one to be cautious in drawing conclusions from work done on the remainder, no matter how carefully done. As it is, all reports are not acceptable when judged by the requirements proposed by Weller, which include an autopsy with complete microscopic study and the elimination of all possibilities of metastasis. For instance, Duguid,[32] who wisely speaks of "primary intrathoracic neoplasms," was able to confirm only 78 of 195 diagnoses by microscopic examination.

Furthermore, certain hospitals and clinics have types of patients who tend to contribute more cases of cancer of the lung than others. This holds where there are low percentages of women and children, because the disease is more prevalent in men past middle life. In our hospital, for example, we have a rate of 2 per cent according to the statistics of autopsies (greater, in fact, than that of general cancer), but it must be noted that we have obtained nearly 100 per cent necropsies in cases in which death occurred from cancer, but only 35 per cent in all cases in which death curred. This gives a rate of about 0.6 per cent of all deaths instead of 2 per cent. Obviously, our figures for general cancer are not high and will give no information of value. Duguid mentioned the unreliability of statistics from teaching institutions, where great zeal is shown in securing the unusual type of case for teaching purposes.

The percentage of cancers of the lung, therefore, may depend largely on what happens in that unknown group of patients not now coming to autopsy, and until we have complete data on that group we must consider the increase only "apparent."

We have attempted to make a useful classification that would serve the purposes of diagnosis and treatment. Thus far therapeutic results have been poor. This is not due so much to the hopelessness of the situation as to diagnostic shortcomings. Recently several reports have shown that operative procedures are effective even when the lesions are advanced, owing mainly to the fact that many metastasize rather late.

70. Lubarsch, O.: Einiges zur Sterblichkeits-und Leichenöffnungsstatistik, Med. Klin. **20**:299, 1924.

71. Karsner, H. T., and Saphir, O.: Small Cell Carcinoma of the Lung, Am. J. Path. **6**:559, 1930.

Harrington,[72] Jackson and his associates [67] and Allen and Smith [73] have given high hopes for favorable surgical effects.

We have rather arbitrarily divided the field into 7 groups, according to the effects produced directly or indirectly. The grouping is as follows:

1. An involvement of the basal layer of the bronchi or bronchioli, causing a cough; slight mucoid expectoration, sometimes blood-tinged, with symptoms only of mild bronchial irritation. There is slight, if any, shadow in the bronchus, and there are no definite physical signs. The diagnosis is established only by a bronchoscopic view or section.

2. Constriction of the lumen of the bronchus. The signs are dyspnea, shortness of breath and more cough than in the first group. There is a diminished breath sound on auscultation distal to the involved region. The shadow in the roentgenogram is definite but variable. The endoscopic view usually shows a fixed bronchus; the bronchoscopic section reveals the tumor if it is on the main bronchi.

3. Parenchymal extension. This is an exaggeration of the preceding process, with metastases into the parenchyma of the lung and regional lymph nodes.

4. Parenchymal extension, presenting signs of cavitation.

5. Pressure on adjacent structures, resulting in dysphagia, stridor, aphonia, irregular pupils and dilated veins in the neck, depending on the structures involved.

6. Pleural involvement with unrelenting pain of a variable character. A diffuse shadow is shown in the roentgenogram, usually due to effusion.

7. Metastases. They are variable, depending on the location, and are caused chiefly by an invasion of the tumor into a pulmonary vein. In metastasis to the central nervous system practically any nervous disease may be simulated.

This grouping may be simplified on the basis of therapeutic possibilities. Accordingly, we rearrange it into 3 groups according to the degree or types of surgical procedure:

1. Simple excision of the primary nodule by means of the bronchoscope, followed by the application of radium (includes most of the cases in group 1 in the foregoing classification).

2. Lobectomy (*a*) when the primary nodule cannot be reached by a bronchoscope (includes a few cases in group 1) or (*b*) when the

72. Harrington, S. W.: Surgical Treatment of Tumors of the Lung and Mediastinum, Surg., Gynec. & Obst. **52**:417, 1931.

73. Allen, C. I., and Smith, F. J.: Primary Carcinoma of the Lung, Surg., Gynec. & Obst. **55**:151, 1932.

condition is more advanced (includes cases in group 2) when the metastases have been only by direct extension (case 6) or locally by way of the lymphatics.

3. Palliative, if at all (includes groups 3 to 7, inclusive).

One is struck by the resemblance of this last grouping to the old classification of tuberculosis into early, moderate and far advanced groups.

SUMMARY

An epidemiologic and clinical study has been made of primary cancer of the lung, with reports of 13 cases, 12 of which were unquestionably primary in the lungs and bronchi and 1 primary in the ovary. There has been an approximately tenfold increase in the number of cases of cancer of the lung coming to autopsy within the last forty years, and a twofold increase in the last ten years. There is no valid evidence, however, to prove an increase in the general incidence of the disease except where there is contact with radioactive dust (Schneeberg and Joachimstal miners). The increase that has occurred may be partly accounted for on the basis of (1) the increased life expectancy from 43 to 58 years in approximately the last half century; (2) a better knowledge of the causes of other pulmonary diseases (e. g., the knowledge resulting from the discovery of the tubercle bacillus); (3) better diagnostic equipment (x-ray apparatus, bronchoscope and similar equipment); (4) increased zeal on the part of the medical profession and laity (better hospitalization, better transportation and other factors); (5) a changed attitude on the part of the pathologists in recognizing as primary carcinomas tumors that were once called metastases and sarcomas. It is not justifiable, therefore, to claim an increase in cancer of the lung until all the unknown factors are studied (such as the relative number of cancers of the lung that occur in rural districts).

The symptoms and clinical findings are reviewed, as well as the diagnosis and the differential diagnosis. For a diagnosis, reliance should be placed on a gradually appearing cough (commonly in men past middle life), followed by a variable but constant pain, and expectoration of sputum frequently streaked with blood, all of which may be accompanied with or followed by dyspnea. Other less common signs are anorexia, fever, loss of weight, symptoms due to pressure (dysphagia and aphonia) and a variety of symptoms due to metastases. The physical signs reveal the presence of a gradually increasing bronchial tumor, with limitation of motion of the affected side, slight or no moisture at first, decreased breath sounds distal to the bronchial obstruction, hyperresonance above, dulness, and ultimately flatness over the tumor. The roentgenogram reveals a gradually progressing growth of tumor out from the hilus or along a bronchus, and the growth may be

diffuse or circumscribed. The endoscopic view reveals a "woody" or fixed bronchus, and study of a bronchoscopic section generally clinches the diagnosis.

The laboratory examination should first reveal a scant or mucoid sputum, sometimes streaked with blood or tinted with hemoglobin, free from tubercle bacilli. Later, tumor cells should be found in the sputum or pleural fluid. Such early findings offer the only opportunity for permanent therapeutic aid.

A pertinent observation has been recorded pertaining to distant metastases from cancer of the lung. They seem to depend on the rapidity and extent of the growth of the primary tumor into a pulmonary vein.

A practical classification is given according to the various stages of the disease and also from the standpoint of diagnosis and therapeutic possibilities.

DIFFUSE ULCERATION OF THE ESOPHAGUS AND TRACHEA ASSOCIATED WITH DIABETES MELLITUS

ABSENCE OF ARTERIOSCLEROSIS

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Diffuse ulceration of the esophagus, of a degree sufficient to produce esophageal symptoms, is very unusual in the absence of obstruction. A lesion of this type was found in the first case that we report. We had not previously observed such diffuse ulceration except at necropsy, when in all probability postmortem changes were at least partly responsible. Similarly, we had not observed diffuse ulcerative tracheitis, as in the second case. That both of these uncommon lesions occurred in persons with diabetes suggests an etiologic factor in the metabolic abnormality. That patients with uncontrolled diabetes have a predilection for infectious diseases is attested by general experience, but, so far as we have learned, the complications considered here have not been reported in the literature on diabetes.

REPORT OF CASES

CASE 1.—*Lesion of the Esophagus.*—A farm laborer, 24 years of age, manifested abruptly the cardinal symptoms of diabetes. Two weeks later, in November, 1924, he was admitted to the hospital, and urinalysis disclosed the presence of large amounts of sugar. The sugar content of the blood was 210 mg. per hundred cubic centimeters. The patient was 68 inches (173 cm.) tall, and weighed 145 pounds (65 Kg.). There was no family history of diabetes or of any other abnormalities of metabolism. The patient had appendicitis at the age of 7 years, for which appendectomy was performed; diphtheria at 17; influenza with pneumonia at 19; a fracture of the jaw from the kick of a horse at 20; acute tonsillitis at 21, and bronchopneumonia at 23.

General examination revealed enlarged tonsils containing pus, slightly enlarged cervical lymph nodes, ichthyotic skin and a systolic murmur over the apex of the heart. The blood pressure in millimeters of mercury was 92 systolic and 64 diastolic. The determination of the basal metabolic rate was + 3 per cent. The patient was instructed to observe dietary restrictions and to use insulin. When he was dismissed from the hospital, the urine was free from sugar, and he was receiving 10 units of insulin daily and a diet of 52 Gm. of carbohydrate, 44 Gm. of protein and 218 Gm. of fat. Tonsillectomy was advised.

The patient did not follow dietary instructions accurately. His wife deserted him, and his family objected to his living with them. He was in poor economic

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circumstances, and lived alone, largely supported by charity. In April, 1925, a physician was called who found him in a "hysterical convulsion." The urine contained sugar; the temperature was 100 F., and the throat was inflamed. There was an odor of whisky in the room. Arrangements to place the patient in an institution for the indigent could not be made.

Three months later, in July, 1925, the patient was brought to the Mayo Clinic and was admitted to the hospital in a state of diabetic acidosis; he was stuporous and complained of abdominal pains; his skin and tongue were dry; he was hyperpneic, and the odor of acetone was strong. The carbon dioxide-combining power of the blood plasma was 10 per cent by volume; the concentration of sugar was 415 mg., and that of urea was 60 mg., per hundred cubic centimeters of blood. This episode had been initiated by the patient's inability to secure the proper diet and by his neglecting to take the regular doses of insulin. The usual measures to combat coma proved effective, and four days later the patient was dismissed from the hospital with instructions to attend an outpatient class for diabetic patients. His attendance was irregular, and at no time was the glycosuria satisfactorily controlled. He did, however, continue to take insulin in doses of from 30 to 50 units daily, and was thereby able to maintain his weight and reasonable strength, and to avoid coma. He remarried, and became the father of an infant in whom diabetes developed at the age of 1 year and 10 weeks. In April, 1929, the patient was apprehended for larceny and was committed to the state penitentiary. The prison attendants are reported to have said that they would "break him of the insulin habit." Three or four attacks of coma occurred when he was in the penitentiary. Three and a half months later, when discharged on parole, he weighed only 100 pounds (45 Kg.), having lost 60 pounds (27 Kg.). During the last few weeks in the penitentiary pain on swallowing appeared in the substernal region; sometimes it was so severe that he could not eat. Solid food had to be washed down with water. The pain was burning, and extended from the sternal notch to the epigastrium. Twice he had vomited blood-stained material. Roentgenograms of the stomach and esophagus did not reveal abnormalities, but on esophagoscopic examination an extensive annular ulceration was seen in the lower half of the esophagus with little, if any, reduction in the lumen of the esophagus. This area was covered with a necrotic membrane and bled easily. The serologic reaction for syphilis had never been positive, and was negative on this examination.

Severe chronic acidosis existed when the patient left the penitentiary, but this was brought under control, and rapid gain in weight and strength followed. The ulceration in the esophagus was treated by the application of a solution of 20 per cent silver nitrate, and by August, 1930, on direct examination, the mucous membrane seemed to be much improved; however, ulceration was still present. The blood pressure on July 21, 1930, was 124 systolic and 90 diastolic.

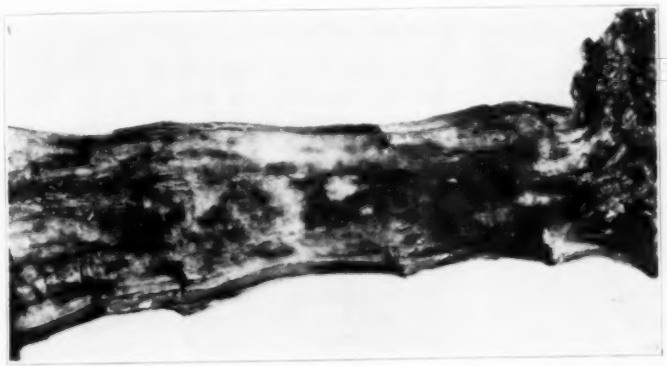
Some time after this, the patient escaped from the surveillance of the police, and in January, 1931, we were informed by a physician of his death in another state from diabetic acidosis. The patient had been in coma for three days. The body was returned to Rochester, Minn., where necropsy was performed. The anatomic findings were diabetes mellitus (clinical) with diabetic coma (clinical), atrophy of the pancreas, bilateral bronchopneumonia and subacute ulcerative esophagitis. The pancreas weighed 32 Gm. and appeared normal, except that it was small (the normal weight is 75 Gm.). The aorta was no more sclerotic than would be expected for a normal person of this man's age. There were a few streaks and patches of fatty infiltration such as we classify as arteriosclerosis, graded 1, but which some observers would not designate as arteriosclerosis.

In the esophagus were numerous superficial areas of ulceration which were more prominent in the lower third; its wall was considerably thickened throughout (see illustration). The stomach and duodenum appeared normal.

Microscopic examination of the pancreas disclosed a slight increase in the connective tissue. The acinar elements, however, including the islands, appeared normal, although the islands seemed fewer than usual. The aortic arch was not abnormal. The intima was unbroken. The vasa vasorum appeared normal.

CASE 2.—*Diffuse Ulcerative Lesion in the Trachea.*—A salesman, aged 57, came to the clinic in June, 1930, because of hoarseness. For seven months he had noticed hoarseness when singing, and for three months, when speaking. For three years, since the extraction of a few teeth, his weight had fallen from 172 to 167 pounds (78 to 75 Kg.). He had diphtheria at the age of 13 years and influenza at the age of 45.

The first twelve-hour specimen of urine was found to contain 30 Gm. of sugar, but no acetone bodies. On first examination, the blood sugar was found to be



Diffuse ulceration of the esophagus associated with diabetes mellitus in the absence of arteriosclerosis.

272 mg. per hundred cubic centimeters with the patient fasting. A diagnosis of diabetes mellitus was made. The serologic test for syphilis gave negative results. Indirect examination of the larynx revealed thickening in the subglottic area, with ulceration and crusting that extended into the trachea. On bronchoscopic examination, a similar condition was found to involve the entire trachea. The ulceration was strikingly similar to that seen in the esophagus of the first patient. It may be noted that there was no history of diabetes or other metabolic disease in the patient's family.

The patient was admitted to the hospital. The diabetes responded promptly to dietary treatment and insulin. A solution of potassium iodide was given by mouth, and the larynx and trachea were treated daily with a spray of mineral oil. When the patient was dismissed, twelve days later, the urine was free from sugar, and the sugar in the blood was 100 Gm. per hundred cubic centimeters, with an intake of food consisting of 73 Gm. of carbohydrate, 53 Gm. of protein and 197 Gm. of fat, and an insulin dosage of 10 units daily. Subsequent reports indicated gradual improvement of the ulcerated trachea.

COMMENT

These cases of diabetes are reported mainly because of the discovery of unusual and, so far as we know, previously unrecognized complications—diffuse ulceration of the esophagus in the absence of any obstructive lesion and a similar ulceration of the trachea. The possibility of an etiologic relationship in the accompanying metabolic abnormality is considered. The first of these cases is also of interest because arteriosclerosis, other than a few patches and streaks of fatty deposits in the intima that would be expected in any man of the patient's age, could not be found at death. Weichselbaum [1] and other investigators have suggested that arteriosclerosis may be the cause of diabetes in many cases in which the two conditions are found accompanying each other, and not, as is usually assumed, the result of diabetes. This case adds strength to such a view. The diabetes was severe; it persisted, with ineffectual efforts at control, for six years; periods of severe acidosis occurred frequently. Under these circumstances, the lipids of the blood must have been abnormally high most of the time, yet arteriosclerosis did not develop to a degree that can be considered abnormal.

1. Weichselbaum, A.: Ueber die Veränderungen des Pankreas bei Diabetes mellitus, Sitzungsb. d. k. Akad. d. Wissensch. Math.-Naturw. Kl. Wien **119**:73, 1910.

HUMAN CAPILLARIES IN HEALTH AND IN DISEASE

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The capillaries constitute a most essential unit of the circulatory system,[1] the part about which least is known. Technical improvements have greatly facilitated capillary studies. The apparatus used for our studies was recently described in detail.[2]

NORMAL CAPILLARIES OF THE SKIN

The first impression one gains in a study of the capillaries is that even when normal they are subject to a wide range of variation, not only in different persons, but within the same person. This is true of all anatomic parts. One must therefore guard against drawing conclusions from small differences in structure or in reaction.

Appearance.—It is known that the capillaries are the finest terminal connecting loops between the arterioles and the venules. Each capillary is divided into a narrow, constricted arterial limb and a wider, more dilated venous limb. The diameter of the arterial side may be less than the diameter of a red blood cell or large enough for several to pass through at once. In the living human being, with the use of reflected light, the walls of the capillaries are invisible, and only the column of blood cells is seen. This has often given rise to erroneous conclusions. Frequently, there is a break in the column of cells and serum alone passes through. The passage of these spaces along the loops has been described as peristaltic waves. This theory will be considered later. The capillary wall consists of an inner endothelial layer and an outer muscular layer. The muscular layer is not continuous, but consists of a widely meshed network of fine fibrils which connect with nucleated cells, first described by Rouget.[3] These cells and fibrils probably make

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Aided by grants from the Josiah Macy, Jr., Foundation.

1. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, 1929.

2. Duryee, A. W., and Wright, I. S.: Modern Methods for the Study of Human Capillaries, Am. J. M. Sc. **5**:664 (May) 1933.

3. Rouget, C.: Mémoire sur le développement de la technique contractile des vaisseaux, Compt. rend. Acad. d. sc. **79**:559, 1873; Sur las contractilité des capillaires sanguins, ibid. **88**:916, 1879.

up the contractile system of the capillaries. There is evidence to show that there is a regulating mechanism controlling these systems, either by a minute connecting nerve fibril or by direct spread of nerve impulses. Vimtrup [4] claimed to have demonstrated Rouget cells in man, but Spalteholz [5] questioned that the nuclei seen by Vimtrup were those of true Rouget cells (Krogh [1]). The average number of these cells per millimeter of animal capillaries is from twenty to fifty. The total length of one cell with its fibrils averages about from 40 to 80 microns.

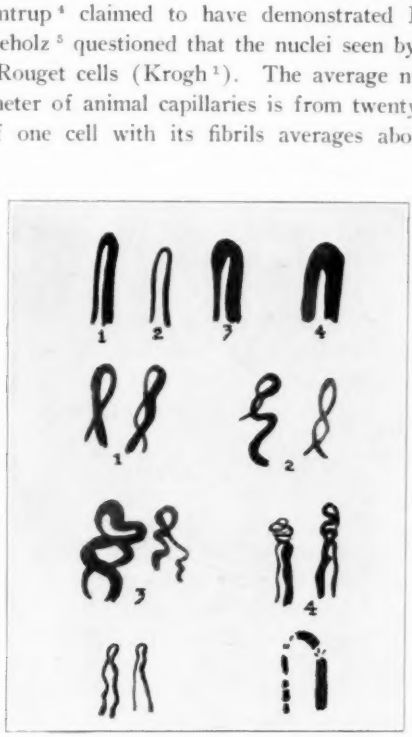

Fig. 1.—Schematic illustration portraying the common morphologic variations in capillaries of the human nail fold. The lowest line represents the "moth-eaten" capillaries in arteriosclerosis and a capillary with breaks in the column of cells which are filled with serum.

The normal thickness of the endothelium appears to be somewhat less than 1 micron (about 0.8 micron).

4. Vimtrup, B.: Beiträge zu Anatomie der Capillaren: I. Ueber contractile Elemente in der Gefasswand der Blutcapillaren, Ztschr. f. d. ges. Anat. **65**:150, 1922; II. Weiter Untersuchungen über contractile Elemente in der Gefasswand der Blutcapillaren, ibid. **68**:469, 1923.

5. Spalteholz, W., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 1, p. 379.

Heimberger [6] stated that the capillary loop in each papilla of the human nail fold is surrounded by a continuous lymph space traversed by a number of threads or septums which keep the loop in position.

He [7] also described short, very fine arteriovenous anastomoses connecting the peripheral arterioles and the venules, short-circuiting the capillaries and used under certain conditions subsequently described. Intracapillary anastomoses may more rarely be seen. These intracapillary anastomoses appear to have the power of going in and out of action independently of the rest of the capillary with which they are connected. This would be further evidence in favor of the presence

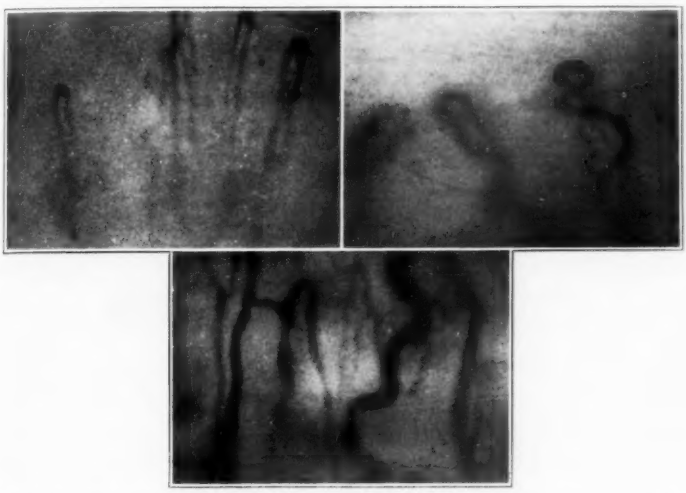

Fig. 2.—Photographs of intracapillary anastomoses. These can be accepted as proved only when cells have been observed to pass from the main capillary loops through these anastomoses. (These and all accompanying photographs are unretouched. They are enlargements made from 35 mm. film on which the magnification is × 60.)

of Rouget cells or their counterpart as emphasized by one of us (Wright [8]).

6. Heimberger, H.: Beiträge zur Physiologie der menschlichen Capillaren: III, Verhalten auf Reizung mit galvanischem Strom, Ztschr. f. d. ges. exper. Med. **51**:112, 1926; Beiträge zur Physiologie der menschlichen Capillaren: V. Färbeversuche am Capillarendothel und die Lymphräume des Papillarkörpergewebes, ibid. **55**:17, 1927.

7. Heimberger, H.: Beiträge zur Physiologie der menschlichen Capillaren, Ztschr. f. d. ges. exper. Med. **46**:519, 1925.

8. Wright, I. S.: Intra-Capillary Anastomoses, J. Clin. Investigation **2**:835 (July) 1932.

The venules and arterioles do not subdivide into capillaries in a uniform manner. In some nail folds the arteriole and the venule can be seen running parallel to the edge of the nail fold with the arteriolar loop of the capillaries branching off at right angles to the arteriole and the venous portion of the capillary loop emptying at approximately right angles into the venule (fig. 3 *A*). We have observed, less commonly, variations from this type in which the arteriolar limb received its blood supply from arterioles which approached in an irregular manner and were indistinctly seen, and the venous portion of the capillary loops emptied into a venule which appeared like the trunk of a tree with several venules emptying into it at different levels and which in its turn emptied into a large venous channel at a deeper level (fig. 3 *B*). Many variations from these common types may be seen.

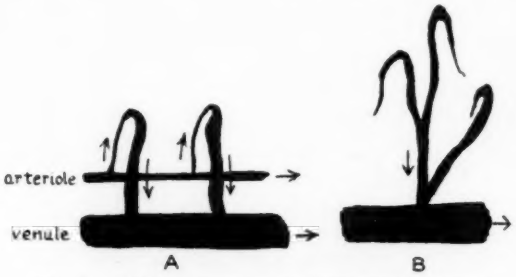

Fig. 3.—Types of arteriole-capillary-venule patterns.

Hagen [9] called attention to a constriction of the capillaries associated with the aneurysmal bulging and a tendency to bleed at the time of the menses. He also suggested changes with the seasons. These claims need much more confirmation.

Age.—The appearance of the capillaries changes with increased age. In new-born infants there is seen a network of capillary tubes which do not definitely appear as loops. With normal development to adulthood, loops gradually appear. These elongate slowly and tend to become somewhat more tortuous as senescence approaches. As will be discussed later, certain pathologic conditions greatly accentuate this. Most adults have scattered, very tortuous loops. These become significant as they increase in number, until in certain conditions described later, practically all of the capillaries are tortuous.

9. Hagen, W.: Die Schwankungen im Capillarkreislauf, Ztschr. f. d. ges. exper. Med. **14**:364, 1921; Periodische, konstitutionelle und pathologische Schwankungen im Verhalten der Blutcapillaren, Virchows Arch. f. path. Anat. **239**:504, 1922; Deutsche med. Wchnschr. **48**:1507 (Nov. 10) 1922.

Cutter and Marquardt [10] showed by means of a negative pressure-producing apparatus that fragility of the capillary walls increases in direct proportion to the age.

Actual Size.—If a capillary is of sufficient diameter to permit the passage of two or more red blood cells at the same time, a definite axial stream is established with a surrounding zone of plasma. As the capillary walls are invisible, it is then difficult to determine the exact size of the capillary in question, although the apparent shape, as shown by the blood stream, remains recognizable under practically all conditions. The large white corpuscles can readily be seen as they come

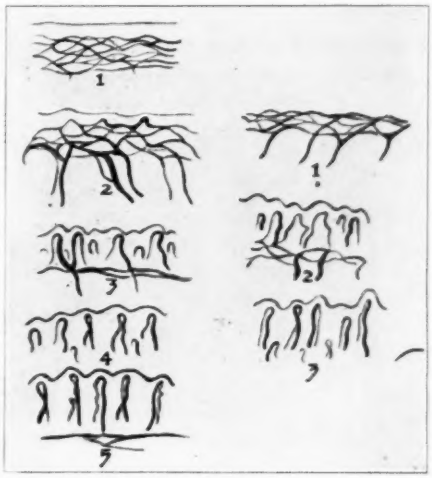

Fig. 4.—Schematic drawings of the development of capillaries in man. Number 1 in each case represents the capillary network in the new-born infant, and the successive sketches show the development to normal adulthood.

along. The statement of average dimensions is futile, as the variations in diameter and in observable length are great.

Globules.—Hinselmann [11] and Klingmüller [12] studied minute bodies which may occasionally be seen just beyond the tips of capillary loops. These globules are transitory, but may be observable on several suc-

10. Cutter, I. S., and Marquardt, G. H.: Studies in Capillary Fragility, Proc. Soc. Exper. Biol. & Med. **28**:113 (Nov.) 1930.

11. Hinselmann, H.: Ein eigenartiges Zirkulationsphänomen bei einer Schwangeren und einer Eklamptischen: Ein Beitrag zur Kenntnis der Kapillaren Blutungen, Deutsche med. Wchnschr. **48**:254, 1922.

12. Klingmüller, M.: Capillarstudien; ueber die Scheitelkügelchen der Nagelfalzcapillaren: III, Ztschr. f. d. ges. exper. Med. **55**:808, 1927.

cessive days. Hinselmann concluded that they were a manifestation of the phenomenon of capillary bleeding, and that they represented a pathologic reduction of resistance of the walls of the capillaries. Klingmüller was able, however, to demonstrate the presence of these globules in normal patients and could produce them by forced running or by a moderate cooling of the skin. He therefore felt that they are not an abnormal finding, but that they prove that the capillaries of the nail cuticle are sometimes considerably wider than is to be expected from the extent of their blood stream. Von Thoma,[13] Herzog [14] and Tannenberg [15] substantiated this belief by work in animals. The globules may be due to pouches such as Herzog [14] noted in the capillaries of the tongue in frogs.

We have recently observed these globules in several capillary loops in one patient. In two of these loops it could clearly be seen that the

Fig. 5.—These capillaries are extremely tortuous for a man aged 30, in apparently perfect health, with a blood pressure of 126 systolic and 74 diastolic. This patient held the Intercollegiate Wrestling Championship, thus having put unusual strain on his circulation. We are not convinced of a definite relationship. It will be interesting to follow this patient for a period of years.

blood cells passing in the axial stream would catch the edge of the small clump of cells making up the globule and rotate the clump. Occasionally the clump would be caught in the axial stream and disappear, but shortly a new clump would be thrown off into the tip of the lumen and would rotate. We consider this definite proof that Klingmüller is correct in his belief that these capillaries may be much wider than can be observed under ordinary conditions.

13. von Thoma, R.: Die experimentell-mathematische Behandlung des Blutkreislaufes, in Abderhalden: Handbuch der biochemischen Arbeitsmethoden, Berlin, Urban & Schwarzenberger, 1909-1910, vol. 4, p. 1103.

14. Herzog, F.: Endothelien der Froschzunge als Phagocyten und Wanderzellen, Ztschr. f. d. ges. exper. Med. **43**:79, 1924.

15. Tannenberg, J.: Ueber die Kapillartätigkeit, Verhandl. d. deutsch. path. Gesellsch. **20**:374. 1925.

Physiology.—1. Function: The function of the capillaries is to permit an easy exchange of gases and fluids essential to the metabolism of the surrounding tissues. The rate of this exchange depends on several factors, one of which has been discussed, namely, the very thin capillary wall.

A second factor is the rate of flow of the blood through the capillaries. This factor also varies in different normal persons and to some degree in different capillaries in the same person. It varies greatly in each person under varying body and environmental conditions. Normally, the flow may be interrupted, and under changing conditions a varying number of capillaries may be in action. If the conditions remain unchanged (room temperature with hand at level of heart), it has been our observation that approximately the same number of capillaries and the majority of the same capillaries remain in action in a given field. Within these, the flow may be continuous over long periods of time, or it may flow, stop, and flow again. Noting great changes in the percentage of time that the flow was actually taking place, we have used what we term a "two minute flow test." For this test, large, easily defined capillaries are used in which blood cells are constantly present. Vessels which contract and disappear are not suitable. The number of seconds of flow and of stoppage are counted in a two minute (one hundred and twenty second) period, with the selected capillary under direct observation. A number of vessels are used to determine the averages and the extremes in a given patient. We have found that, under the foregoing conditions, normal variations in the period of stoppage average from fifteen seconds to zero in two minutes (one hundred and twenty seconds), whereas pathologic conditions may produce a period of stoppage as high as sixty-four seconds in one hundred and twenty seconds. In certain conditions of vascular spasm, no flow may be noted in a two minute period. In our patients with high blood pressure we rarely have seen stoppage of the flow in the large, well defined capillaries. Changes found in other conditions are being studied. The test provides a rough estimation of the constancy of flow, and examples of its practical value will be quoted later.

Stewart [16] estimated that, traveling at the rapid rate of 0.5 mm. per second, it would take 1 c.mm. of blood over six hours to pass through a capillary 10 microns in diameter. This slow process explains the necessity for the small arteriovenous anastomoses to accomplish rapid changes in the temperature of the skin.

2. Contractility: The ability of the capillaries to contract independently or to produce peristaltic movements have long been debated points.

16. Stewart, G. N.: Manual of Physiology, London, Baillière, Tindall & Cox, 1895, p. 59.

The work of Lewis [17] and his co-workers would tend to indicate that the capillaries and the venules are capable of active contraction. These vessels are capable of exerting a force when fully contracted which resists the full entry of blood into them up to a pressure of from 90 to 100 mm. of mercury. When dilated, they are able, by contracting, to expel their contents against internal pressures of at least from 50 to 60 mm. of mercury. This means that these vessels must be of almost as great import as the arterioles in influencing circulatory events.

Hooker,[18] after an exhaustive review of the literature and his own studies,[19] concluded that the capillary bed had the ability to respond to the local needs of the tissue by dilatation when the conditions of the tissue tend toward asphyxiation and by constriction when the local needs have been satisfied.

The capillary bed is responsive to chemical influences by local reactions, usually by dilatation (only in special or pathologic cases by general reactions), and to nervous stimulation usually by constriction, over the body as a whole. It is therefore likely that beyond the arterioles the capillaries and venules function actively, thereby participating directly in vascular reactions. Further studies are necessary to establish this as a fact.

In this paper no attempt will be made to discuss in detail the reactions of the capillaries to various drugs and to foreign substances or to trauma.

If the capillaries are capable of active contraction, it is important to determine whether they aid in the propulsion of blood by peristaltic waves. Klingmüller [20] felt that the convolutions which are observed along the sides of the blood stream and which have been attributed to the peristaltic contraction of the walls of the capillaries by Kylin [21] and others are gaps in the flow of the blood cell columns or bulgings in the instance of over-filled capillaries. Our observations have led us to agree with Klingmüller on this point.

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17. (*a*) Cotton, R. F.; Clade, J. G., and Lewis, T.: Observations upon Dermatographism with Special Reference to the Contractile Power of the Capillaries, Heart **6**:227, 1915-1917. (*b*) Lewis, T.: The Force Exerted by the Minute Vessels of the Skin in Contracting, ibid. **11**:109, 1924; The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927. (*c*) Lewis, T., and Haynal, I.: Observations Relating to the Tone of the Minute Vessels of the Human Skin, ibid. **14**:177, 1928.

18. Hooker, D. R.: Evidence of Functional Activity on the Part of the Capillaries and Venules, Physiol. Rev. **1**:112, 1921.

19. Danzer, C. S., and Hooker, D. R.: Determination of the Capillary Blood Pressure in Man with the Micro-Capillary Tonometer, Am. J. Physiol. **52**:136, 1920.

20. Klingmüller, M.: Capillarstudien; I. Mitteilung zur Frage der Capillarperistaltik, Ztschr. f. d. ges. exper. Med. **46**:94, 1925.

21. Kylin, E.: Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926.

3. Pressure: Many methods for the determination of the capillary blood pressure in man have been advanced since Roy and Brown [22] first published their fundamental observations in 1878. By these methods the normal capillary blood pressure has been determined to be from 7 to 70.5 mm. of mercury. Friedenthal [23] was justified in his conclusions that in 1922 the determination of capillary pressure by most of the existing methods was of little practical significance. The principle of the von Kries [24] method was used in most of the methods up to 1922. This consisted in applying a small glass plate to the skin and determining the pressure necessary to produce paling. We now know that the capillary flow may still be active at such a point, and that the color of the skin is largely controlled by the venous plexuses lying in the dermis. Von Kries published his normal readings as 37.7 mm. of mercury. Hough and Ballantyne,[25] using the same method, published from 40 to 50 mm. of mercury as their normal readings. Kylin,[26] in 1919, and Danzer and Hooker,[19] in 1920, introduced methods by which the flow of blood in the capillaries is observed while the pressure is being taken. The Danzer-Hooker capillary tonometer (described in detail in their communication) permits the observer to increase the pressure gradually until he notes a stoppage in capillary flow. There may then be a to-and-fro-movement of the blood, or it may even flow in the reverse direction. As the pressure is lowered, the point at which the blood flow resumes its forward movement is accepted as the capillary pressure. The average findings of various workers using this method have agreed closely, varying between 19 and 26 mm. of mercury. Our average normal readings have fallen within these limits.

A new tonometer has been demonstrated during the 1931 Graduate Fortnight of the New York Academy of Medicine by Strax and DeGraff. The capillaries are under direct observation with this method also. Strax and DeGraff suggested as the capillary pressure point the pressure at which the blood flow slows as it passes through the lumen. We feel that the use of this end-point would increase the many variables to a considerable degree, as the blood flow is constantly slowing and

22. Roy, C. S., and Brown, J. G.: The Blood Pressure and Its Variations in the Arterioles, Capillaries and Smaller Veins, Arch. f. Anat. u. Physiol. (Physiol. Abt.) 1878, p. 158; J. Physiol. **2**:323, 1879.

23. Friedenthal, H.: Ueber Kapillardruck Bestimmung, Ztschr. f. exper. Path. u. Therap. **79**:222, 1917.

24. von Kries, N.: Ueber den Druck in den Blutcapillaren der menschlichen Haut, Arb. a. d. physiol.-anstalt-Leipzig **10**:69, 1875.

25. Hough, T., and Ballantyne, B.: Preliminary Note on the Effects of Changes in External Temperature on the Circulation of Blood in the Skin, J. Boston Soc. M. Sc. **3**:330, 1899.

26. Kylin, E.: Proceedings, Ninth Nordiske Congress of Internal Medicine, Copenhagen, 1919.

speeding up again. Frequently it slows to the point of stoppage. We have found that when the blood flow has been stopped by pressure and that pressure is released, the blood immediately begins to flow again (with rare exceptions). We therefore agree with Danzer and Hooker that the point of pressure at which the flow recommences tends to introduce fewer inaccuracies and should be accepted as the capillary pressure when taken by such methods.

Landis [27] recently introduced a method for the determination of capillary pressure which from the point of view of scientific observation will probably force all other methods now known into discard. He cannulates the capillaries by means of fine glass pipets, and by direct observation determines the exact point at which the corpuscles oscillate in and out of the tip of the pipet. The pressure rises in one third of the capillaries for one or two minutes, but returns to normal in from three to five minutes.

Whereas all other methods determine one figure as the capillary pressure, Landis has been able to demonstrate that there is a definite

Capillary Pressure Readings of Landis

Pressure Measured	Position of Pipet	Number of Observations	Capillary Pressure, Mm. Hg	
			Range	Average
Arteriolar limb	A	125	21-48	32
Summit of loop	B	19	15-32	20
Venous limb	C	99	6-18	12

gradient of pressure fall in the capillary loop. His readings, based on different portions of the loop, are shown in the table. Three readings taken in the same loop at points A, B and C confirm these figures. The importance of this gradient in controlling tissue fluids will be discussed later.

The figures obtained by the Danzer-Hooker tonometer seem to represent about an average of the three figures. The method of Landis requires an elaborate technic, so that other methods may continue in use for rough estimations of capillary pressure, but they should not be accepted as giving the true picture of the pressures within a capillary. For the purpose of accurate comparison, all pressure readings should be taken with the hand at the cardiac level and under standard conditions.

4. Permeability: The permeability of the capillaries is of great importance in its effect on the fluid balance of the body. Ganzzlen [28]

27. Landis, E. M.: (*a*) Micro-Injection Studies of Capillary Blood Pressure in Human Skin, Heart **15**:209, 1930; (*b*) Micro-Injection Studies of Capillary Blood Pressure in Raynaud's Disease, ibid. **15**:247, 1930.

28. Ganzzlen, Max: Ueber die Durchlassigkeit der Haargefässwand beim Menschen, München. med. Wchnschr. **69**:263, 1922.

first introduced the method now in use for its determination. A small cantharides plaster is applied to the arms of the patient, and the transudate in the blister is examined by a refractometer. The contents of the blister normally show albumin 5.04 per cent (Reiss exudate table). Blood serum normally contains 8.06 per cent albumin (regular serum table). Petersen and Willis [29] suggested a formula for the permeability ratio:

$$\text{Permeability ratio} = \frac{\text{percentage of blister protein}}{\text{percentage of serum protein}}$$

Since the time necessary for the production of the blister varies greatly in pathologic conditions, the following formula was deduced:

$$\text{Inflammatory index} = \frac{\text{permeability ratio}}{\text{blister time}}$$

Normal blister time is from seven and one-half to eight hours. The results of Petersen and Willis,[29] Petersen and Levinson [30] and Chasanow [31] showed the average permeability ratio to equal from 0.62 to 0.68.

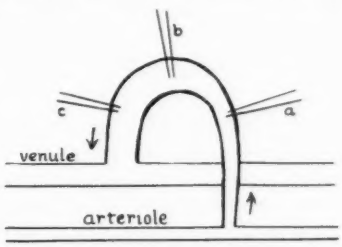

Fig. 6.—Drawing illustrating Landis' points for reading capillary pressure.

The permeability of the capillary walls is subject to the laws of filtration, diffusion and osmosis and is also affected by the ionic concentration at the cell membranes in the blood, the state of the endocrine system, and especially, according to Bruck,[32] Kayikawa,[33] Petersen and Willis [29] and Chasanow,[31] the state of the visceral nervous system.

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29. Petersen, W. F., and Willis, D. A.: Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, Arch. Int. Med. **38**:663 (Dec.) 1926.

30. Petersen, W. F., and Levinson, S. A.: The Skin Reactions, Blood Chemistry and Physical Status of "Normal" Men and of Clinical Patients, Arch. Path. **9**:205 (Jan.) 1930.

31. Chasanow, M.: Permeabilität der Hautkapillaren bei Nervenkranken, Monatschr. f. Psychiat. u. Neurol. **75**:62, 1930.

32. Bruck, C.: Experimentelle Beiträge zur Aetiologie und Pathogenese der Urticaria, Arch. f. Dermat. u. Syph. **96**:241, 1909.

33. Kayikawa, J.: Untersuchungen über die Permeabilität der Zellen: X, Biochem. Ztschr. **133**:391, 1922.

Rous, Gilding and Smith,[34] Smith and Rous,[35] and McMaster, Hudack and Rous [36] showed by the intravenous use of dyes (Chicago blue 6 B, trypan red, trypan violet and trypan blue) that the permeability of capillaries in the skeletal muscles of mammals increases progressively along their course and is greatest when they pass into the least venules. This gradient helps to equalize the opportunities to cells along the course of the capillaries. It is probably due to a structural differentiation along the capillary. The venules are even more permeable. Slight increases in venous pressure increase the outward passage of dyes from the venules and the venous limb of the capillaries. As this pressure is increased, the greater permeability extends along the capillary toward the arteriolar end. It is impossible to say whether this is due to secondary dilatation of the capillaries producing an increase in the surface area with local permeability due to thinning of the wall or to heightened hydrostatic pressure producing active filtration. Probably both factors contribute. If venous pressure is increased to the point of nearly equaling the arteriolar pressure producing forcible dilatation of the capillaries, the gradient of vascular permeability disappears. These workers feel that transudation through small venules is more important for the rapid development of edema of the skin as a result of increased venous pressure than is transudation through the capillaries.

In heart disease with failure, for instance, the small vessels are caught between the arterial pressure and an abnormally high venous one. Most of the edema fluid actually accumulates in the subcutaneous tissue. It seems more likely, though not proved, that it seeps back secondarily from the skin rather than arises as a result of fluid escaping from the relatively infrequent subcutaneous vessels.

Edema following vascular injury by heat or cold, on the other hand, develops mainly as a result of loss of fluid by the capillaries, the permeability of which rises to equal or exceed that of the venules.

Hoff and Leuwer [37] experimented with the use of 1 per cent solution of congo red intravenously, and found that this high molecular dye practically did not penetrate the wall of the capillary, under normal

34. Rous, P.; Gilding, G. P., and Smith, F.: The Gradient of Vascular Permeability, J. Exper. Med. **51**:807, 1930.

35. Smith, F., and Rous, P.: Conditions in Frog and Chicken Muscle and in the Mammalian Diaphragm, J. Exper. Med. **53**:195, 1931; Gradient Along the Capillaries and Venules of Frog Skin, ibid. **53**:219, 1931.

36. McMaster, P. D.; Hudack, S. S., and Rous, P.: The Relation of Hydrostatic Pressure to the Gradient of Capillary Permeability, J. Exper. Med. **55**:203, 1932; McMaster, P. D., and Hudack, S. S.: The Vessels Involved in Hydrostatic Transudation, ibid. **55**:417 and 431, 1932.

37. Hoff, F., and Leuwer, W.: Experimentelle Untersuchungen über die Permeabilität der Capillaren des Menschen, Ztschr. f. d. ges. exper. Med. **51**:1, 1926.

conditions, but that the same dye penetrated the wall in an inflamed field. Therefore, there is an increase in permeability of the capillary walls in the inflamed region.

The production of a wheal by the injection of various substances such as sodium chloride, potassium chloride, calcium chloride, magnesium chloride, casein and a nonspecific milk preparation also produces changes in the permeability of the capillaries to congo red.

5. Osmosis: The downward gradient of capillary pressure demonstrated by Landis appears to be of great significance in the control of fluid exchange. Determinations of the osmotic pressure of the colloid for human serum and plasma vary between 23 and 28 mm. of mercury (Govaerts,[38] Serr,[39] Schade and Claussen,[40] Iversen and Nakazawa,[41] Verney [42]). Dieter [43] gave as his figure 31 mm. of mercury.

The figures of Landis show that the pressure in the arterial limb of the capillary under normal conditions is greater than the osmotic pressure of the plasma proteins; hence, other factors being equal, the direction of flow should be outward from the capillary wall. The venous limb has a pressure below the normal osmotic pressure of the plasma proteins; hence the flow should be inward through the wall of the capillary. Such conditions as increase the capillary pressure throughout a capillary above the osmotic pressure of the plasma (example, heating of the skin) result in greatly increased rates of filtration and production of lymph. With dilatation of the arterioles and capillaries, the arteriolar fraction of peripheral resistance is reduced, and as a result the level of capillary pressure in both the venous and the arteriolar limbs of the capillary loop is raised to the point where outward filtration may take place in both portions of the loop. In this instance we have increased pressure plus increased outward filtering area with a decreased absorption area, the result being increased tissue fluid plus increased lymph flow.

Capillary pressure is thus clearly demonstrated to be an important factor in the normal and abnormal interchange of fluid between the

38. Govaerts, Paul: Recherches cliniques sur le rôle de la pression osmotique des proteines du sang, dans la pathogenie des oedemes et de l'hypertension artérielle, Bull. Acad. roy. de méd. de Belgique **4**:161, 1924.

39. Serr, H.: Blutbeschaffenheit und Glaukom, Arch. f. Ophth. **114**:393, 1924.

40. Schade, H., and Claussen, F.: Der onkotische Druck des Blutplasmas und die Entstehung der renal-bedingten Oedeme, Ztschr. f. klin. Med. **100**:363, 1924.

41. Iversen, Paul, and Nakazawa, Fusakichi: Ueber die Biochemie des Filtrations Odems, Biochem. Ztschr. **191**:307, 1927.

42. Verney, E. B.: The Osmotic Pressure of the Proteins of Human Serum and Plasma, J. Physiol. **61**:319, 1926.

43. Dieter, Walter: Ueber den Zusammenhang zwischen osmotischem Druck, insbesondere Kapillardruck und Augendruck nach neuen experimentellen und klinischen Untersuchungen, Arch. f. Augenh. **96**:179, 1925.

blood and the tissue spaces. The downward gradient of capillary pressure and the upward gradient of permeability must act in proper balance for the equalization of opportunity for all cells.

6. Response to Heat, Cold, Stroking and Changes in Altitude: For a number of years Lewis [44] has been studying the effects of slight injuries on normal capillaries. He has reached the following conclusions:

1. Light stroking of the skin produces white lines due to active contraction of the capillaries and venules of the skin.

2. Heavy stroking of the skin produces red lines due to active dilatation of the capillaries and venules, also possibly the terminal arterioles.

(*a*) The surrounding flush is due to independent and widespread dilatation of the arterioles brought about by local axon reflex.

(*b*) The wheal is due to an outpouring of fluid from the vessels secondary to a local increase of the permeability of the vessel walls independent of dilatation and uncontrolled by the nervous system. A dilution of 1 : 30,000 of histamine when injected into the skin produces the same triple response. Probably the same fundamental cause is at work, namely, a histamine-like substance (termed the H substance).

The effect of increased environmental temperature is the dilation of the capillaries with an increase in the rate of blood flow through them. With fever, these effects are greatly accentuated. When the environmental temperature is lowered slowly, the number of capillaries remaining open and active usually decreases and the rate of flow usually slows. However, we have found that if the part is suddenly chilled, as by dipping in ice water, the effect in some cases may be the activation of many more capillaries with a markedly increased rate of flow. This is apparently an attempted compensatory reaction.

Although the theoretical freezing point of skin is about —0.6 C. (as physiologic solution of sodium chloride), arctic explorers may be exposed to —20 or 30 C. without frostbite. The relative moistness and greasiness of the skin predispose to a protective supercoating.

Vannotti,[45] of von Willer's laboratory, studied the effects of altitude on normal capillaries. He has found that with changes in altitude (hence atmospheric pressure) up to 4,560 meters, as with changes in temperature, and effects of the toxic products of metabolism produced by exercise and fatigue, certain changes take place in the diameter and form of the capillaries, and also in the rate of flow through them. Morphologically, it is interesting and important that the characteristic

44. Lewis, T.: Abstract of Four Croonian Lectures, Brit. M. J. **2**:61 (July 10) 1926. Lewis.[17d]

45. Vannotti, A.: Die Wirkung des Hohenklimas auf die Hautcapillaren der Menschen, Klin. Wchnschr. **6**:253 (Feb. 7) 1931.

shape of each capillary loop remains recognizable despite the action of these various factors. Definite changes can, however, be noted in separate parts of the loops. With increased altitude, the capillaries become dilated and fill with blood. This change is undoubtedly associated with the transient polycythemia commonly noted in mountain climbers at high altitudes. The capillaries apparently attempt to approximate their condition at normal level but are affected by the increased heart rate and probably other little understood factors. The reestablishment of normal appearance and diameter on return to sea level after a variable time at a high altitude takes place by degrees and follows the changes which can be noted in the organism as a whole in its transition to normal function under the new conditions.

CAPILLARY CHANGES IN DISEASE CONDITIONS

High Blood Pressure.—While a markedly increased blood pressure is frequently associated with an increase in tortuosity of the capillaries

Fig. 7.—The variability of the appearance of capillaries in cases of hypertension. The tortuous loops are from a patient with an average blood pressure of 190 systolic and 120 diastolic. The straight loops are from a patient with the unusual blood pressure of 300 systolic and 190 diastolic. In both cases the flow was very rapid and uninterrupted. The arterial limbs were constricted and the outlines distinct.

—definitely more pronounced than would be expected from the age of the patient—there are many exceptions to this rule. We cannot confirm Grzechowiak,[46] who described characteristic changes occurring in different stages of the disease. We have not seen an increase in tortuosity above normal in patients with uncomplicated hypotension. Therefore, we may assume that some factors which are present in patients with hypertension may produce tortuosity under certain conditions, and that these conditions or these factors are practically never found in patients with uncomplicated hypotension. One cannot say what these

46. Grzechowiak, F.: Der Kapillardruck, besonders während der Schwangerschaft, Ztschr. f. Geburtsh. u. Gynäk. **87**:128, 1924.

factors are at present. Boas and Mufson [47] classified cases of hypertension into two groups which cannot be differentiated clinically: those with high capillary blood pressure and those with normal or low capillary blood pressure. The capillaries in these cases may appear as tortuous with low capillary pressure as with high pressure. As an example, in beds alongside of each other at the New York Post-Graduate Hospital were a man aged 39 and one aged 82. The young man was suffering from malignant hypertension. His blood pressure averaged 220 systolic and 140 diastolic; his arteries were sclerosed wherever palpable, his capillaries were very tortuous, but not markedly dilated, and the capillary pressure averaged 26 mm. of mercury (Danzer-Hooker tonometer). The old man's blood pressure varied between 188 systolic and 92 diastolic and 140 systolic and 70 diastolic. His peripheral arteries were not unusually sclerosed, even for a man fifteen years younger, and his capillaries were much less tortuous than the young man's. In fact, they would have been normal for a man fifteen years younger than he was. His capillary pressure averaged 22 mm. of mercury. The readings of the capillary pressure for both were within normal limits.

High capillary pressures were present in seventeen of forty-five cases of hypertension reported by Boas and Mufson.[47] The mortality in this group was much higher (eight of seventeen, or 47 per cent) than in the group with low readings (five of twenty-eight, or 17.8 per cent). Four patients with high and four with low capillary pressure came to autopsy. No characteristic differences were noted.

In general, the most significant relationship established was between the capillary pressure and the diastolic blood pressure. However, many of the patients of Boas and Mufson and many of our patients with a high diastolic pressure have had a normal capillary pressure. A much larger group of patients must be studied to establish this work satisfactorily.

These workers reported one unusual case showing a normal blood pressure from 125 systolic and 95 diastolic to 105 systolic and 70 diastolic and with a high capillary pressure averaging about 33 on the basis of many readings. Capillary pressure bears no fixed determinable relationship to arterial or venous pressure, and workers such as von Farkas [48] and Nakazawa and Izumi,[49] who attempt, to calculate the

47. Boas, K., and Mufson, I.: The Capillary Blood Pressure in Arterial Hypertension and in Nephritis, J. Lab. & Clin. Med. **9**:152 (Dec.) 1923.

48. von Farkas, G.: Ist das Oedem ein Resultat der Capillarsekretion, Ztschr. f. d. ges. exper. Med. **62**:35, 1928.

49. Nakazawa, Fusakichi, and Izumi, Jiro: Studien über den kolloidosmotischen Druck des Bluts im normalen und pathologischen Zustand, Tohoku J. Exper. Med. **16**:341, 1930.

capillary pressure from either of these figures, can only draw unjustified conclusions.

Petersen found nine patients with hypertension with a systolic pressure of over 140 in the group with less permeability; four patients showed increased permeability.

Weiss and Frazier [50] found no definite increase in the number of active capillaries per square millimeter of body surface in persons with hypertension as compared with the normal controls. In studying the number of active capillaries in a unit area of skin, however, it is difficult to estimate other important signs of activity, such as the rate of flow and dilatation or constriction of the capillary limbs. This difficulty is due to the fact that only the tips of the capillaries can be seen, except in such special areas as the junction of the skin and mucous membrane of the lips and at the nail fold.

The rate of flow through the capillaries of most hypertensive patients is increased, and with the "two minute test" previously described it is rare to find a stoppage longer than four seconds in any of the large capillaries. Often with prolonged observation no stoppage can be noted.

Low Blood Pressure.—Conversely with high blood pressure, a consistently low blood pressure is usually associated with long, straight, dilated capillary loops. Through these the blood cells flow slowly, frequently stopping. The capillary pressure is low or normal. In one case, the average stoppage in the "two minute flow test" was sixty-six seconds. This patient was referred to us because of tingling and burning of the fingers, for which no definite cause could be found by the internist or neurologist. Her blood pressure at that time was 85 systolic and 65 diastolic, but many persons with low blood pressure do not have the symptoms of which this patient complained. She was put on a regimen of alternating hot and cold water baths twice a day and sent to the seashore to tone up generally. She returned after five weeks with complete freedom from her symptoms. At this time her average stoppage was four seconds. Her blood pressure was 110 systolic and 65 diastolic.

We do not feel that the difference of a few seconds more or less has any significance in the two minute flow test. When the blood is flowing through major capillaries less than half of the time by measurement, as in this case, we feel that such a fact is important and should be noted according to some standard. Ten counts should be made on different prominent capillaries and an average obtained.

50. Weiss, S., and Frazier, W.: The Density of the Surface Capillary Bed of the Forearm in Health, in Arterial Hypertension, and in Arteriosclerosis, Am. Heart J. **5**:511 (April) 1930.

Essential low blood pressure may conceivably be due to capillary dilatation and stasis secondary to a toxin. Histamine shock, as well as other types of shock, present the same picture. Friedlander [51] expressed the belief that the H substance may be responsible.

Acute Nephritis.—It seems probable in view of the studies of many workers that acute glomerulonephritis should be looked on as a manifestation of a pathologic condition in which the capillaries generally show evidence of damage. During the acute stages there is a consistent elevation in capillary pressure (Kylin [52] and Mufson [53]). This returns to normal with convalescence. Kylin found that in scarlet fever with complicating acute glomerulonephritis the capillary pressure increases successively for several days before the onset of albuminuria. In some cases the capillary pressure increased and subsided without the presence of albuminuria. In cases with no increased pressure, nephritis did not

Fig. 8.—This illustrates the usual straight, moderately dilated capillaries seen in a patient with uncomplicated hypotension. The flow was slow with frequent stoppage. The average blood pressure was 100 systolic and 60 diastolic.

develop. Pathologically, the primary lesion of the kidney is found in glomerular capillaries. Hückel [54] was of the opinion that the reason that all of the glomeruli are not affected is the fact that many are inactive a large portion of the time, and hence would not be exposed to toxins circulating in the blood. The active glomeruli would be the first affected. The edema seen must be due to increased permeability of the capillary walls, increased capillary pressure or decreased osmotic pressure of the serum proteins. The last is probably secondary to the loss of albumin, since it remains normal in mild cases. The cause of

51. Friedlander, A.: Address at Graduate Fortnight of New York Academy of Medicine, New York Post-Graduate Medical School, Oct. 19, 1932.

52. Kylin, E.: Die Hypertoniekrankheiten, Berlin, Julius Springer, 1930.

53. Mufson, I.: A Study of the Capillary Pressure in Nephritis and Hypertension, Am. J. M. Sc. **183**:632 (May) 1932.

54. Hückel, R., cited by Kylin.[52]

these capillary changes is unknown, but it seems likely that absorption of toxins from foci of infection plays a large rôle.

A similar diffuse capillary poisoning has been demonstrated by Heubner [55] with the use of gold chloride, resulting in dilatation with hematuria and edema.

No constant morphologic change has been noted in the capillaries in this condition. In our experience, the rate of flow and the constancy of flow have increased as would be expected with the increased pressure.

Chronic Nephritis.—The capillaries in chronic nephritis show increased tortuosity in many cases. This tends to increase with the duration of the disease and the hypertension present. In Mufson's [53] series there was a correlation between the capillary pressure and the degree of renal dysfunction. Nearly all of the cases with normal capillary pressure showed normal renal function, while those showing

Fig. 9.—Capillaries in a patient with marked generalized arteriosclerosis. They showed the typical "moth-eaten" appearance, with a slow flow and frequent stoppage.

increased capillary pressure showed increasingly impaired function. There were occasional exceptions both ways. These findings also point to a systemic capillary involvement, although in these cases it would seem to appear after the early changes in the kidney as evidenced by urinary findings.

In reference to contradictory data concerning the capillaries in hypertension and nephritis, Patzold [56] called attention to the fact that since the venous and capillary systems are from the same anlage, conflicting opinions may arise from studies of the capillaries without a consideration being given to the status of the venous system at that time.

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55. Heubner, Wolfgang: Ueber Vergiftung der Blutcapillaren, Arch. exper. Path. **56**:370, 1907.

56. Patzold, A.: Untersuchungen über das menschliche Venensystem, Deutsches Arch. f. klin. Med. **171**:89 (April) 1931.

Senile Arteriosclerosis.—In patients with hardening of the peripheral arteries and without any other demonstrable disease, we have noted no unusual degree of tortuosity. These cases fall into the senescent groups and are entitled to moderate tortuosity because of age. The blood flow becomes sluggish as the condition becomes more marked. The loops sometimes appear rather moth-eaten. Weiss and Frazier [56] found that no definite relationship existed between the number of capillaries active per millimeter of body surface, and the clinical evidence of arteriosclerosis or the age of the patients. They concluded that a reduction in number of visible surface capillaries per square unit cannot be held responsible for the changes in the skin with the advancing age and in arteriosclerosis. We have noted, however, that the rate and constancy of flow are frequently diminished in these cases, and such findings may well account for changes in the skin and elsewhere with age.

Toxemia at Pregnancy.—Capillary pressure in normal pregnancies is normal according to Grzechowiak [57] and Nevermann,[58] but with toxemias the capillary pressure tends to rise. Mufson [59] summarized three groups of patients as follows: (1) Normal gravida with normal capillary morphology and pressure. These mothers had uneventful deliveries and were delivered of normal children. (2) Women with hypertension but low capillary pressure readings during pregnancy. These mothers responded to conservative routine treatment. There was one fetal death. (3) Women with high capillary pressure readings during pregnancy. The course of the pregnancy was stormy and the response to treatment was poor in 70 per cent of the mothers, with resultant therapeutic induction of labor. Fetal death occurred in 50 per cent of these cases.

It is clear that high capillary blood pressure readings have a serious import for the mother and fetus.

Polycythemia Vera.—The active capillaries in polycythemia vera are increased in number. Brown and Giffin [60] and Brown and Sheard [61] studied this increase quantitatively with the following results: There

57. Grzechowiak, F.: Die medikamentose Beeinflussung des Kapillarkreislaufes am Fingernagelfalz, Monatschr. f. Geburtsh. u. Gynäk. **62**:7, 1923.

58. Nevermann, H.: Capillardruckmessungen, Klin. Wchnschr. **3**:1433 (Aug. 5) 1924.

59. Mufson, I.: The Capillary Pressure in the Toxemias of Pregnancy, Am. J. Obst. & Gynec. **15**:800, 1928.

60. Brown, G. E., and Giffin, H. Z.: Studies of the Vascular Changes in Cases of Polycythemia Vera, Am. J. M. Sc. **171**:157 (Feb.) 1926.

61. Brown, G. E., and Sheard, C.: Measurements of the Skin Capillaries in Cases of Polycythemia Vera and the Role of Those Capillaries in the Production of Erythrosis, J. Clin. Investigation **2**:423 (June) 1926.

was an average of from sixty-two to sixty-five open capillaries for each square millimeter of skin on the back of the hand (normal figure, from fifteen to forty). No marked variation was noted in any one subject.

By use of photomicrographs, the area of exposed capillary blood per unit area of skin was calculated. This ratio averaged 15 per cent in the cases of polycythemia vera, which is three times greater than the normal figure of 4.9 per cent. In our cases no increase in tortuosity has been noted. In fact, the loops are usually very straight. They appear to be filled and bulging with cells which move sluggishly through the lumen.

By way of contrast, a patient with a relative polycythemia secondary to a congenital cardiac condition (red blood cells 8,340,000; hemoglobin 111 per cent) showed markedly tortuous capillaries.

In the cases of true polycythemia the venous limb becomes especially dilated, which dilatation seems gradually to work back over the crest of

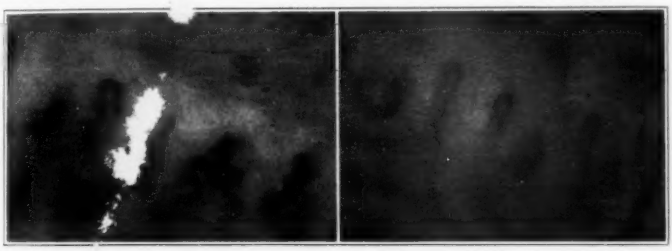

Fig. 10.—The straight capillaries are from a patient with polycythemia vera, with 10,6[illegible]0 red blood cells and 123 per cent hemoglobin. Dilatation extending from the venous side over into the arterial limb could be seen. The very tortuous and dilated capillaries are from a patient with congenital heart disease with secondary relative polycythemia, with 8,000,000 red blood cells and 128 per cent hemoglobin. We have never seen marked tortuosity in a case of uncomplicated polycythemia vera.

the loop. The arterial limb is usually normal and may even be slightly constricted.

In the cases which respond to treatment, the number of active capillaries decrease and they appear less prominently.

Scleroderma.—The capillaries in patients with scleroderma are difficult to study in the areas affected. They appear as irregular distorted vessels. Rarely are they seen as definite loops but rather as hazy shadows through which the blood flows slowly and stops when the environmental or body temperature is lowered. The blood then becomes cyanotic, but if the temperature is raised the flow is quickened and the blood becomes brighter red. Because of the texture of the skin, capillary pressure readings are not possible.

Brown, O'Leary and Adson [62] ascribed the marked impairment in the transparency of the skin to the following three factors: (1) the increased density in the skin, (2) perhaps the interference with flow of lymph and accumulation of the fluid and (3) pigmentation.

A major factor in a well advanced case is lack of blood in the skin. This lack of blood is probably due in a large measure to two factors: the increase in collagen, which results in shutting down of the capillaries and arterioles by pressure, and an excessive degree of vasospasm in the arterioles. The foregoing authors have demonstrated that sympathetic ganglionectomy helps the condition as a whole and that the capillaries become much more prominent and active, hence, insuring an increased blood supply to the area involved.

Raynaud's Disease.—The capillaries of the nail bed in Raynaud's disease between attacks are long, dilated, characteristically atonic loops through which the blood flows slowly, frequently stopping. The number

Fig. 11.—Remarkable dilatation of the capillaries during the period of hyperemia in Raynaud's disease. As will be noted, the dilatation is most marked on the venous side.

open per field is greater than normal. The response to changes in temperature is marked. In a case described by Adson and Brown [63] after sympathetic ganglionectomy the capillaries on the side on which operation had been performed were reduced to normal in number and appearance; the blood flow was regular and the blood red. The loops were more restricted, showing increased tonus.

Landis,[27b] using his micropipet, studied the changes in the capillary pressure in Raynaud's disease. During the period of spasm the capillary pressure at the summit of the loop falls to from 5 to 8 mm. of mercury. If the arterial inflow has stopped, this pressure is probably due to pressure in the veins of the hand or forearm.

62. Brown, G. E.; O'Leary, P., and Adson, A. W.: Diagnostic and Physiologic Studies in Certain Forms of Scleroderma, Ann. Int. Med. **4**:531 (Dec.) 1930.

63. Adson, A. W., and Brown, G. E.: Raynaud's Disease of the Upper Extremities, J. A. M. A. **92**:444 (Feb. 9) 1929.

During the first eight to twelve minutes of recovery, with its accompanying hyperemia, the capillary pressure rises, reaching maximal pressures of from 32 to 45 mm. of mercury, and then gradually falls to more normal readings. During the period of spasm, there are no pulsation in the pipet and no sensation of throbbing. During the period of hyperemia, there are marked pulsation and marked throbbing. During a normal period there are diminished pulsation and throbbing. The skin temperature is dependent on the room temperature during the period of spasm. With recovery, it rises definitely above room temperature gradually returning to normal.

During the spasm, the capillaries are sharply defined through flat tissues. During recovery, the outlines of the capillaries gradually become blurred, and the skin at the base of the nail becomes visibly raised. This is due to the accumulation of fluid in the hyperemic tissue.

Probably the high pressure recorded plus increased permeability due to asphyxia explains the swelling of the fingers during recovery.

In studies to determine the situation of the vascular spasm in Raynaud's disease, Landis found that when a pneumatic cuff was inflated to 40 mm. of mercury in normal persons the capillary pressure rose to an equal height within from three to four minutes. In Raynaud's disease, the rise was very slow. During the first four to five minutes there was no change, and only after thirteen to fifteen minutes was the capillary pressure equal to that in the armlet. This showed that inflow is retarded on the arterial side. When the pressure of the cuff was released, the capillary pressure fell so rapidly that it was almost normal in one minute.

The facts that the veins in the hands are small when the hands are cold and blue and that the pressure falls rapidly under the conditions described in the foregoing paragraph show that the obstruction offered by these veins is insufficient to interfere with outflow from the capillaries.

These observations, together with the low pressures observed during spasm, show that the stasis in Raynaud's disease is not due to venous congestion. It is due to changes in the arterial side of the loop.

Thrombo-Angiitis Obliterans—Buerger's Disease.—The pronounced rubor which is noted in this and other diseases marked by defective circulation in the deeper vessels is secondary to the condition of the capillaries and venules. In agreement with Brown, Allen and Malhorner,[64] we find that these cases seem to be divided according to capillary changes into two groups. In the first group—without vasoconstrictor phenomena—the capillaries are moderately dilated and the number open

64. Brown, G. E.; Allen, E. V. A., and Malhorner, H. R.: Thrombo-Angiitis Obliterans, Philadelphia, W. B. Saunders Company, 1928.

and active is increased. The flow is slow, often stopping. It may cease for an entire two minute period. If the extremity is lowered below the heart level, the rubor increases and more capillaries and venules can be seen to open. Cyanosis occurs with further slowing of the capillary flow.

The second group with visible vasoconstrictor phenomena have been more common in our series. At room temperature or colder, there is a marked constriction of the capillaries. Only a few per field may be indistinctly visible. Photographing these capillaries has been especially difficult, an indistinct blur representing each capillary. The flow is slow and the blood becomes cyanotic. If the environmental temperature is raised, capillary flow slowly increases in rate and a few more capillaries open. The reaction is slow, and the increase is not great until the temperature reaches a high level. The flow does not become regular, but is jerky with many gaps. The foregoing authors have

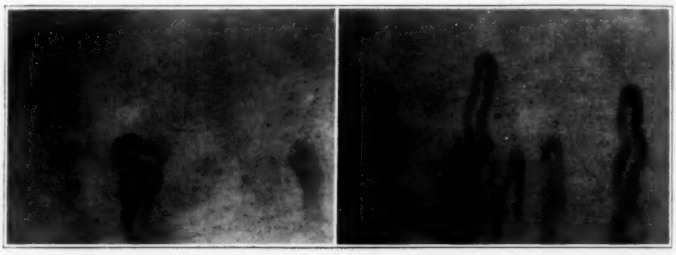

Fig. 12.—Variations in appearance of the capillaries in arthritis. These and the ones in the photograph showing the most marked anastomoses (fig. 2) are from Dr. Kovacs' series of cases of arthritis.

suggested that this effect may be due to a precapillary arteriole opening and closing, allowing small spurts of blood to pass through. Tests with epinephrine, pituitary and histamine showed that the capillaries in this condition are not paralyzed, but require greater stimuli to produce vasoconstriction. Many of these small vessels show actual thrombosis on pathologic section.

Erythromelalgia.—The capillary loops in erythromelalgia may be gigantic, grotesque and irregular in form. The blood flow is exceedingly sluggish, and stagnant pools of blood may form at the ends of the capillaries, helping to produce the changes in the color of the skin seen in this condition.

Arthritis.—There has been great disagreement concerning the characteristics of the capillaries in arthritis. Kovacs,[65] working in the

65. Kovacs, J., with the collaboration of Wright, I. S., and Duryee, A. W.: The Surface Temperature and Minute Blood Vessels of the Skin in Arthritis, J. A. M. A. **100:**1018 (April 1) 1933.

capillary laboratory at the New York Post-Graduate Medical School and Hospital, recently completed a detailed study of this subject. He concluded that poor capillary circulation could not be established as the direct cause of the pathologic changes accompanying this disease. The only consistent findings were the decrease in number and the constriction of capillaries in fingers with Hebreden's nodes or swollen joints (this could be accounted for on the basis of mechanical pressure) and a lowered surface temperature. In other cases there was nothing characteristic in the number, appearance, rate or consistency of flow. His cases were subdivided into rheumatoid arthritis, osteo-arthritis and non-articular rheumatism and were studied separately. It is conceded that the condition of the capillaries of the skin may not indicate the condition of the capillaries within a bone or a joint. It seems that conclusions drawn on the assumption that comparisons can be made should be

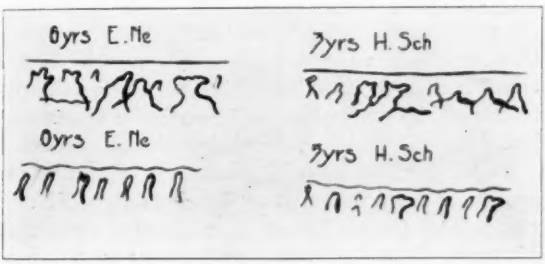

Fig. 13.—The effect of the administration of thyroid extract to cretins (Jaensch).

accepted with great skepticism. Kovacs' study should help to reestablish balance in this field of endeavor.

Relationship Between Capillary Development and Mental Development.—Jaensch and co-workers [66] have been engaged in studies of the developmental processes of the capillaries and their psychophysical relations for some years past. The capillaries of normal infants form a network running horizontally under the surface of a smooth corium. During the course of the first year of infant life, these vessels tend to change from the horizontal capillaries without loops to a more vertical position, forming loops that go up into papillae which rise up from the corium. A difference can then be noted between the arterial and the venous limbs. Parallel with these capillary developments is the development of the child. With stunting of capillary development, it was observed that the child is likewise stunted in all other respects. Jaensch was of the opinion, therefore, that the development, restriction

66. Jaensch, W.; Wittneben, W.; Hoepfner, T.; von Leupoldt, C., and Gundermann, O.: Die Hautkapillarmikroskopie, Halle, A. S., Carl Marhold, 1929.

of development or diversion of development of the capillary field is a fair indication of the state of the individual, especially during the earliest periods of life.

The capillaries of cretins with a low degree of development, i. e., a 16 year old cretin girl who showed the intelligence of a backward 5 year old child and was bodily helpless, show the very early form of capillary development described, which is termed the "archicapillary form." In other words, parallel with the lack of capillary development there has been a lack of mental and physical development. If thyroid given to these children at an early stage is successful in improving their mental and physical status, it can be observed that the capillaries likewise become more normal. If the patient is too old to yield to treatment, the capillaries do not improve so markedly, although they may show relatively more improvement than the mental or the physical status. Jaensch felt that the prime cause for this state of abnormality of the capillaries rests in the inter-relationship between the midbrain, which plays the chief rôle, and the endocrine glands, of which the thyroid gland is the most important. It was found that in districts in which goiter is prevalent, such as Hessen, capillary differentiation is slower even in a normal child than it is in nongoitrous districts, such as Frankfort-on-the-Main. In the latter city the differentiation of infantile capillaries reaches the normal hairpin form in the sixth month of life.

A comparison of the capillaries of pupils of a normal elementary school with those of pupils in an accessory school for the mentally deficient gave the following figures: In the normal school of twenty-six pupils, only three showed capillary restriction, whereas in the accessory school of twenty-one pupils, fourteen showed capillary restriction. From this it would seem that not all feebleminded children have abnormal capillaries and some normal children may have abnormal capillaries.

Among pupils of a normal school in a cretinous district, the percentage of children with restricted capillaries was almost as high as that among pupils of an accessory school in a healthy district.

Gesell [67] stressed the importance of this early developmental stage as follows: "One month of early childhood is of dynamic importance to the developmental economy of the individual. One month of constitutional retardation during a period of two months' time in a child's life, guarantees to the individual spiritual inferiority."

Hoepfner [66] showed that in a group of schools of varying rank, the higher the school the higher the percentage of superior capillaries and that the lower the school rank, the higher the percentage of inferior capillaries.

67. Gesell, A.: Monthly Increments of Development in Infancy, Pedagog. Sem. & J. Genet. Psychol. **203**:32, 1925.

Jaensch and his co-workers were of the opinion that close observation of the capillaries in early childhood should be a state measure, as vaccination is, and is of comparative importance to the fighting of infectious diseases. In this instance, we are concerned with the crippling of human beings with mental inferiority and "moral insanity."

So much importance has been attached to this work that the government of Meresburg in Germany has prepared a questionnaire for use in its school system, regarding the psychophysical condition, past history, family history and capillary findings of the school children.

The conception of "vasoneurosis capillaries" is an important contribution of the Tübingen Clinic under the guidance of O. Müller.[68] Certain neurasthenic persons are commonly recognized by their abnormal pallidity or redness of the skin, frequent changes of the color of the skin, easy and quick irritation of the skin after mechanical irritation, acrocyanosis and similar conditions. These vasoneurotic persons are inclined to urticarial states and bleeding, i. e., small hemorrhages of the skin, vicarious menstrual bleeding, intestinal oozing and frequent epistaxis. Many neurasthenic persons do not fall into this group.

The capillaries of some of these vasoneurotic persons exhibit strange and fantastic forms with many intracapillary anastomoses. Observing the flow, one sees stasis, rapidity and frequent intermittency. All of this points to a change in the tonicity of the vascular system, caused by a disorder of interplay between the vagus and the sympatheticus, which leads to an irregular blood supply of the tissues.

Griffith [69] found an occurrence of these grotesque capillary forms in eight of five hundred cases in which there was no evidence of organic peripheral vascular lesions. In thirty-one of five hundred cases the diagnosis was functional neurasthenia. The eight cases in which vasoneurotic capillaries were shown were included in the thirty-one cases of neurasthenia.

Jaensch [70] showed the close relationship between these vasoneurotic capillaries and those showing retarded development as seen in cretinism and other psychopathic states.

68. Müller, Otfried: Die Kapillaren der menschlichen Korperoberflache in gesunden und kranken Tagen, Stuttgart, Ferdinand Enke, 1922; Die Naturwissenschaft, Berlin, Julius Springer, 1929; Ueber den praktischen Wert der Kapillarpathologie, Deutsche med. Wchnschr. **56**:574 (April 4) 1930, Parrisius, W.: Kapillarstudien Vasoneurose, Deutsche Ztschr. f. Nervenh. **72**:310, 1921

69. Griffith, J. Q., Jr.: The Frequent Occurrence of Abnormal Cutaneous Capillaries in Constitutional Neurasthenic States, Am. J. M. Sc. **183**:180, 1932.

70. Jaensch, W., in Brugsch and Lewy: Die Biologie der Person, Berlin, Urban & Schwarzenberg, 1931, vol. 2, p. 954.

Retarded development of the capillaries is also to be noted in cases of mongolian idiocy. Leader [71] found more marked evidence of retardation and pathologic status of the capillaries as the intelligence and physical development were more markedly subnormal.

Powdermaker [72] claimed that children with deficient physical development accompanied by arrested mental development showed pathologically developed capillaries, while Leader [71] found that eighteen children with delayed physical development but normal or superior intelligence showed normal capillaries.

In a study of capillary circulation in the affected psychoses, Sheveleff [73] observed that in depressions the extremities were moist, cold and cyanotic. The capillaries were easily seen. The loops were thickened and widened. Definite retardation in the rate of flow and frequent aneurysms were noted. There was some evidence of diapedesis. Giant loops were seen.

In cases of mania there was no stasis of blood. The extremities were normal in color. The capillaries were not elongated and no aneurysms were seen.

Studies were made by the injection of methylene blue (methylthionine chloride, U.S.P.) into the field of microscopic vision. In normal persons the dye disappeared in two hours. In persons suffering from depressions it took six hours to disappear, while in patients with mania it disappeared in one and one-half hours.

The effects of pilocarpine and epinephrine intradermally injected were also studied. If the capillaries were dilated, pilocarpine produced no effect, but epinephrine produced a marked vasoconstriction with improvement in circulation. Atropine would act in the same manner. When the capillaries were constricted, epinephrine gave no results, but pilocarpine would produce dilatation of the capillaries with the formation of aneurysms. This would last from twenty to sixty minutes. Sheveleff gained the impression that the capillary picture is different in various types of affective psychoses.

Permeability of the Capillaries in Nervous Disorders.—Chasanow [31] made a study of the permeability of skin capillaries in nervous disorders. In twenty-three (75 per cent) of thirty cases of epidemic encephalitis, the permeability index was increased. The blister time was prolonged in twenty-one of twenty-six cases (80 per cent) to from ten to fourteen hours. The permeability index was considerably

71. Leader, S. D.: Capillary Microscopy in Children, Am. J. Dis. Child. **44**: 403 (Aug.) 1932.

72. Powdermaker, F.: Capillary Forms in Relation to Certain Problems in Development, Arch. Neurol. & Psychiat. **22**:1207 (Dec.) 1929.

73. Sheveleff, N. A.: A Study of Capillary Circulation in the Affective Psychoses, Zhur. Neuropatol. i Psychiat. **8**:53, 1931.

increased in eight (80 per cent) of ten cases of multiple sclerosis. The blister time was prolonged to an average of twelve hours for all.

Mesodermal Syphilis.—In five of eight cases of mesodermal syphilis the permeability index was normal, but it was considerably increased in three cases in which there were manifestations of meningitis. The blister time was prolonged in seven of these cases to from ten to twelve hours. In tabes dorsalis, it was shortened to from five to six hours. In the ectodermal form, the permeability index was increased in three of four cases (75 per cent).

Diseases of the Vessels of the Central Nervous System.—The permeability index was increased in seven cases of this type (all acute)

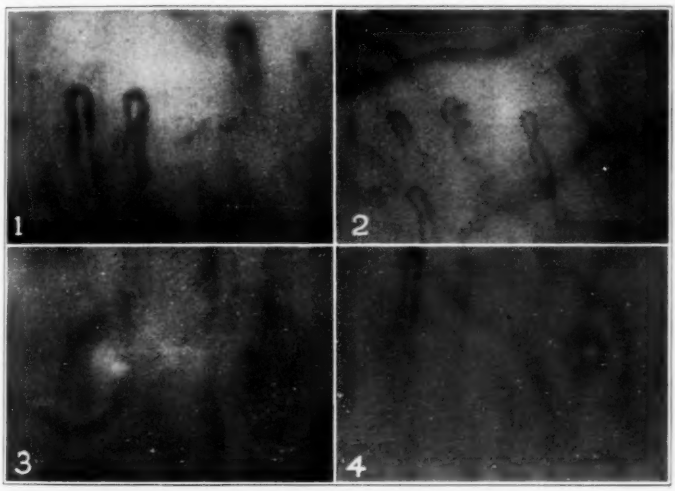

Fig. 14.—Capillaries from four persons with marked clubbing of the fingers. The case of relative polycythemia (fig. 10) offers further variation in this condition. These five cases show the great differences in appearance, number in action, visibility and stoppage which forced us to conclude that there was no definite connection between circulation of the blood and clubbing of the fingers. The primary factors were as follows: *1,* congenital heart disease; *2,* chronic pulmonary osteoarthropathy; *3,* plexiform epithelioma of left main bronchus; *4,* splenectomy thirteen years before (relation?).

and normal or decreased in two cases (chronic), 80 per cent. Blister time was prolonged to from ten to twelve hours.

Diseases of the Peripheral Nerves.—The permeability index was normal or decreased in chronic cases and increased in acute cases. The blister time was nearly normal in the chronic cases but always prolonged in the acute cases.

Tumors of the Central Nervous System.—The permeability index was subnormal in all but two cases of tumor of the central nervous system, and in these two it was above normal. The blister time was prolonged in all of the cases, giving a low inflammation index.

Clubbing of the Fingers.—A relationship of the circulation of the blood to clubbing of the fingers and toes has long been an accepted theory. Duken [74] claimed that a definite capillary pattern exists in cases of clubbing due to chronic pulmonary disease. He described the vessels as long, tortuous, spastic, but as a whole dilated. He stated that there was an increase in number with a granular flow but no stasis. Leader [71] claimed that a definite capillary picture develops in the preclubbing stage if clubbing is going to develop, so that it is possible to prognosticate in this regard. His cases were all in children and included conditions diagnosed as bronchiectasis, pulmonary abscess and chronic cardiac disease.

One of us (Wright [75]) recently presented the results of a similar study in adults. The cases included examples of congenital cardiac disease, abscess of the lung, tumors of the lung of bronchiogenic, endothelial and unknown origin and chronic pulmonary osteo-arthropathy. All the patients had marked clubbing of the fingers. Those with congenital cardiac disease uniformly presented markedly dilated capillaries packed with cells and showing a sluggish flow. Some of these showed increased tortuosity; others did not.

In the other groups there were no uniform findings whatever. Some of those who had the most advanced clubbing of the fingers showed normal capillary pictures, and all variations of rate of flow, tortuosity, size and adult types were found. The fact that clubbing may accompany congestion of the capillaries in congenital cardiac disease and in some other diseases cannot lead to the inference that capillary changes are responsible for clubbing or vice versa, but only that they are coincidental findings. As greatly congested, stagnant capillaries may be present in nail folds of patients for years without the development of clubbing of the fingers, and as the nail fold capillaries of many patients with advanced clubbing of the fingers appear normal in all respects, serious doubt may be entertained as to any definite relationship between these two conditions. Other explanations for clubbing of the fingers, such as disturbance in the lymph drainage, changes in local or general metabolism or the presence of toxic products, are thus far also without scientific proof.

74. Duken, J.: Das Krankheitsbild der Broncheitektasie im Kindesalter, Ergebn. d. inn. Med. u. Kinderh. **34**:457, 1928.

75. Wright, I. S.: Some Observations of Human Capillaries, presented before Section of Medicine, New York Academy of Medicine, March, 1932.

SUMMARY

An endeavor has been made to review present knowledge concerning human capillaries in health and in many specific diseases. Where our experience has justified, we have added our findings or criticized the findings of others. The field is relatively undeveloped, and it may be expected that present theories will be discarded in the near future, and that many additional pathologic processes will be studied from the point of view of the capillary circulation. No discussion of capillary changes in diseases of the skin has been undertaken, since that subject is vast in itself and has been little studied to date. We have also avoided a detailed discussion of capillary reactions to stimuli. Studies in this field are being undertaken and will be reported at a later date.

MONOSODIUM THYROXINE, DESICCATED THYROID AND AN IMPURE SODIUM SALT OF THYROXINE

COMPARISON OF THEIR EFFECTS WHEN ADMINISTERED ORALLY WITH THE EFFECT OF THYROXINE INJECTED INTRAVENOUSLY IN AN ALKALINE SOLUTION

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In 1926 we gave some Squibb's thyroxine for oral use to two patients with low basal metabolism for a few days in doses of from 2 to 10 mg. daily and, having observed no effect, were content to conclude that the current opinion about its lack of effect when administered by mouth was correct. However, as time went on, it seemed worth while to give the matter more serious study.

A review of the literature reveals some difference of opinion as to whether or not thyroxine is effective when administered by mouth. Swingle, Helff and Zwemer,[1] by observing the weight and pulse rate, Burmeister,[2] by observing the weight and urinary output, and Abelin,[3] Schneider,[4] and Boller and Högler[5] (Schering's thyroxine), on the basis of determinations of basal metabolism, concluded that thyroxine is virtually without effect when administered by mouth to normal human beings. Weiss[6] observed no effect in some cases of obesity, although in others it appeared to affect the weight slightly. These observers

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1. Swingle, W. W.; Helff, O. M., and Zwemer, R. L.: The Effect of Thyroxin and Its Acetyl Derivative on Amphibians and Mammals, Am. J. Physiol. **70**:208, 1924.

2. Burmeister, E. A.: Klinischer Beitrag zur Thyroxinfrage, München. med. Wchnschr. **75**:1073, 1928.

3. Abelin, I.: Zur Kenntnis der Thyroxinbestandteile der Schilddrüse, München. med. Wchnschr. **75**:685, 1928.

4. Schneider, E. A.: Ueber die Thyroxinwirkung, Deutsche med. Wchnschr. **54**:1561, 1928.

5. Boller, R., and Högler, F.: Klinische Erfahrungen mit Thyroxin, Thyropurin and Thyreoidin, Klin. Wchnschr. **8**:1297, 1929.

6. Weiss, R. F.: Bedeutet die Einführung des synthetischen Thyroxins in die Schilddrüsenbehandlung der Fettsucht einen Fortschritt? Deutsche med. Wchnschr. **54**:2056, 1928.

apparently used a sodium salt of thyroxine, except Swingle, Helff and Zwemer, who used pure thyroxine also. Gaddum[7] reported pure *l*-thyroxine to be without effect on the oxygen consumption of the rat when given by mouth.

On the other hand, there have been reports that thyroxine has some effect when it is administered by mouth. Plummer,[8] Boothby, Sandiford, Sandiford and Slosse,[9] Schittenhelm and Eisler,[10] Knipping,[11] Zondek and Köhler,[12] Aschner,[13] and Klein[14] observed some effect on the basal metabolism in patients with myxedema, and Snell, Ford and Rowntree[15] and Fonio and Scheurer[16] observed some effect in cretins. Some effect on the oxygen consumption in normal human beings was observed by Grawitz and Dubberstein,[17] Baur and Loewe,[18] Auerbach and Klein,[19] Boller and Högler[5] (one case with Henning's thyroxine) and Klein.[14] Some effect on the basal metabolism in obesity was

7. Gaddum, J. H.: Quantitative Observations on Thyroxine and Allied Substances: II. Effects on the Oxygen Consumption of Rats, J. Physiol. **68**:383, 1930.

8. Plummer, H. S.: Interrelationship of Function of the Thyroid Gland and of Its Active Agent, Thyroxin, in the Tissues of the Body, J. A. M. A. **77**:243 (July 23) 1921.

9. Boothby, W. M.; Sandiford, I.; Sandiford, K., and Slosse, J.: The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects: I. A Method of Studying the Reserve or Deposit Protein with a Preliminary Report of the Results Obtained, Ergebn. d. Physiol. **24**: 728, 1925.

10. Schittenhelm, A., and Eisler, B.: Ueber die Wirksamkeit des Thyroxins (Schering) bei Endokrin bedingten Störungen, Klin. Wchnschr. **6**:1935, 1927.

11. Knipping, H. W.: Ergebnisse der Gasstoffwechseluntersuchung für die Klinik, Klin. Wchnschr. **7**:49, 1928.

12. Zondek, H., and Köhler, G.: Klinische Erfahrung mit synthetischem Thyroxin, Med. Klin. **24**:328, 1928.

13. Aschner, B.: Ueber Thyroxintherapie und ihre Indikationen, Ztschr. f. klin. Med. **114**:360, 1930.

14. Klein, B.: Ueber die hohe Wirksamkeit peroral verabreichten Thyroxinnatriums bei normalen und hypothyreotischen Individuen, Ztschr. f. klin. Med. **119**:477, 1932.

15. Snell, A. M.; Ford, F., and Rowntree, L. G.: Studies in Basal Metabolism, J. A. M. A. **75**:515 (Aug. 15) 1920.

16. Fonio, A., and Scheurer, G.: Ueber die Wirkung des Thyroxins und des Jodes in einer dem Jodgehalt des Thyroxins entsprechenden Dosierung auf einige Abschnitte des Stoffwechsels, auf das Blut usw. bei endemischen Kretinen, Mitt. a. d. Grenzgeb d. Med. u. Chir. **42**:467, 1931.

17. Grawitz, E. R., and Dubberstein, W.: Klinische Prüfung des synthetischen Thyroxin-Henning, Klin. Wchnschr. **7**:797, 1928.

18. Baur, H., and Loewe, G.: Ueber die Wirkung des synthetischen Thyroxins beim Menschen mit normaler Schilddrüse, Deutsches Arch. f. klin. Med. **159**:275, 1928.

19. Auerbach, L., and Klein, B.: Vergleichende Untersuchungen über die Wirksamkeit synthetischer Schilddrüsenpräparate, Klin. Wchnschr. **8**:2332, 1929.

observed by Weiss [6] and Hellfors; [20] some effect on the weight in obesity, by Zondek and Köhler; [12] some effect on the oxygen consumption of rats, by Abelin; [3] and some effect on the oxygen consumption of one dog, by Kunde.[21] Hunt [22] noted that it protected white mice against acetonitrile, and Cameron and Carmichael,[23] that it produced some reduction in the growth rate of rats, as well as hypertrophy of the heart, liver, kidneys and suprarenals and decrease of the growth rate of the thyroid. Lipschitz and Girndt [24] and Krogh and Lindberg [25] showed that it reduced the weight of guinea-pigs.

A few quantitative observations have been reported. In 1921, Plummer [8] reported that "a daily oral dose of 1.6 mg. of thyroxin [1.1 mg. of iodine] will hold the basal metabolism of most thyroidless individuals within normal limits." In contrast with this, the maintenance dose of desiccated thyroid was 130 mg., an amount which contained about 0.26 mg. of iodine. In 1924, Plummer and Boothby [26] made the statement that "desiccated thyroid has been found to be absorbed from the gastro-intestinal tract with greater regularity than has the impure sodium salt of thyroxin. In fact, the absorption of the latter in persons with low basal metabolic rates which we do not attribute to myxedema is very erratic." Boothby, Sandiford, Sandiford and Slosse [9] concluded that 1.6 mg. daily of an impure sodium salt held the basal metabolism of a thyroidless person (basal metabolism, minus 40 per cent) at a level of about zero and 0.8 mg. daily at a level of minus 15 per cent. The dose of 1.6 mg. daily was administered for thirteen days and the dose of 0.8 mg. for twenty-one days after the basal metabolism had been raised to normal by two intravenous injections of thyroxine of 7 mg. each. Kunde [21] gave a dog from 4 to 15 mg. of Kendall's pure crystalline thyroxine daily for eighty-one days and noted a maximum increase of basal metabolism of 119 per cent on the seventieth day. Schittenhelm and Eisler,[10] using Schering's thy-

20. Hellfors, A.: Beitrag zur systematischen Entfettungskur mittels Thyroxin, München. med. Wchnschr. **78**:826, 1931.

21. Kunde, M. M.: Studies on Metabolism: VI. Experimental Hyperthyroidism, Am. J. Physiol. **82**:195, 1927.

22. Hunt, R.: The Acetonitril Test for Thyroid and Some Alterations of Metabolism, Am. J. Physiol. **63**:257, 1923.

23. Cameron, A. T., and Carmichael, J.: Contributions to the Biochemistry of Iodine: IV. The Effect of Thyroxin on Growth in White Rats and in Rabbits, J. Biol. Chem. **46**:35, 1921.

24. Lipschitz, W., and Girndt, O.: Wertbestimmung von Schilddrüsenpräparaten des Handels, Arch. f. exper. Path. u. Pharmakol. **159**:259, 1931.

25. Krogh, M., and Lindberg, A. L.: Studies on the Thyroid Gland: II. The Physiological Activity of Iodine in Thyroxin and in Normal and Pathological Thyroid Glands, Acta path. et microbiol. Scandinav. **9**:21, 1932.

26. Plummer, H. S., and Boothby, W. M.: Glandular Therapy: Administration of Thyroid Preparations, J. A. M. A. **83**:1333 (Oct. 25) 1924.

roxine, noted greater effect in a case of myxedema from 12 mg. of thyroxine intravenously than from 45 mg. by mouth, and in another case, about the same effect from 84 mg. by mouth as from 16 mg. intravenously. All quantities recorded were given in divided doses over a short period, and tablets were used for oral administration. Grawitz and Dubberstein [17] produced an increase in basal metabolism of from 27 (minus 13 to plus 14 per cent) to 48 (minus 35 to plus 13 per cent) points in four patients by administering Henning's thyroxine tablets in doses which varied from 18.5 mg. in two weeks to 57 mg. in four weeks. They concluded that 1 mg. of thyroxine was the equivalent of 0.2 Gm. of thyreoidin. Schneider [4] noted that the metabolism rose from zero to plus 20 per cent during the administration of thyroxine to nine patients, in doses varying from 14 mg. in seven days to 72 mg. in fourteen days. He concluded that the oral administration of 2 mg. daily produced an uncertain and transient rise.

Zondek and Köhler [12] apparently held the basal metabolism of one patient with myxedema at the normal level by administering 1 mg. of synthetic thyroxine (Roche) daily by mouth after the basal metabolism had been raised to normal by giving thyroxine intravenously, whereas in another patient with myxedema the basal metabolism dropped while she was receiving 2 mg. daily by mouth. In obese patients a marked loss in weight occurred while from 8 to 10 mg. was being administered daily. Weiss [6] used from 6 to 8 mg. of Roche's synthetic thyroxine daily in the treatment of obesity and thought it produced less toxic effects than thyreoidin. In some cases of obesity that were refractory to treatment with thyroid, he found that from 0.6 to 0.8 Gm. of thyreoidin Merck daily was effective when from 10 to 12 mg. of thyroxine was actionless. Baur and Loewe [18] came to the conclusion that synthetic thyroxine (Roche) subcutaneously or by mouth in human beings with normal thyroid function had the same action as approximately one hundred times that amount of dried thyroid. Auerbach and Klein [19] concluded that Roche's synthetic thyroxine had only about one-half as much effect when given by mouth as when given intravenously. Harington and Salter,[27] in their paper on the isolation of a polypeptide of thyroxine by tryptic digestion, reported that Gaddum found that "the oral administration of 1 mg. *per diem* for 6 days of pure *l*-thyroxine had practically no effect on the oxygen consumption of a rat, whilst an equivalent dose of the digestion product (1.3 mg. *per diem* for 6 days of a preparation containing 50 per cent of iodine) produced an increase in the oxygen consumption of 85 per cent. By the subcutaneous route, on the other hand, single doses of 1 mg. of *l*-thyroxine and

27. Harington, C. R., and Salter, W. T.: The Isolation of *l*-Thyroxine from the Thyroid Gland by the Action of Proteolytic Enzymes, Biochem. J. **24**:456, 1930.

1.3 mg. of the digestion product caused increases in the oxygen consumption of 32.5 per cent and 37.5 per cent respectively. . . ." Hellfors,[20] by giving comparatively large doses of thyroxine in a short time (e. g., 41.5 mg. in seventeen days) to obese patients, concluded that 0.5 mg. of thyroxine Henning raised the basal metabolism 2 per cent; 2 mg. of thyroxine Schering, 1 per cent; 1 mg. of synthetic thyroxine (Roche), 1 per cent, and one tablet of thyreoidin Merck (0.1 Gm.), from 1 to 3 per cent. Klein[14] recommended that in the treatment of myxedema from 3 to 4 mg. daily be used for the first two or three weeks and then from 1 to 2 mg. daily. In one patient, she produced an increase in the basal metabolism from minus 12 per cent to plus 10 per cent by administering 222 mg. of thyroxine (Schering's tablets) in thirty-seven days; in a second patient, an increase from minus 14 per cent to plus 19 per cent by administering 138 mg. in twenty-six days; in a third patient, an increase from plus 8 to plus 28 per cent by administering 75 mg. in sixteen days; in a fourth patient, an increase from plus 1 to plus 16 per cent by administering 72 mg. in twelve days, and in a fifth patient, an increase from minus 4 to plus 10 per cent by administering 30 mg. in five days. Greater effects were obtained by giving Hoffmann-La Roche's alkaline solution for oral administration, Schering's thyroxine in alkaline solution and Schering's tablets, which are said to contain dialkali salts of thyroxine. Indeed, Klein concluded that thyroxine when given in suitable form and dose has the same effect orally as parenterally. Baur and Loewe[18] likewise concluded that it was more effective by mouth if given in alkaline solution, especially if the solution was markedly diluted.

The observations reported create the impression that thyroxine is effective by mouth when given in tablet form, but is less effective than when given intravenously in alkaline solution. However, there are no adequate data for comparing their effects quantitatively by these two methods of administration. One of the chief difficulties with the data already reported is that the effect by a given route has been observed over too short a period. Our data suggest that it is sometimes necessary to wait several months before the metabolism reaches a level during the administration of a given dose. Moreover, the precise form in which thyroxine was administered was not stated in most instances. Gaddum[7] used pure *l*-thyroxine. Kunde[21] used the pure crystalline thyroxine of Kendall. Plummer and Boothby[26] used an impure sodium salt of thyroxine which represented the acid-insoluble fraction after the preliminary hydrolysis with sodium hydroxide in the separation of thyroxine from the thyroid gland. Because of variations that may result in a product obtained by approximately the same chemical procedure, Plummer[28] does not feel sure that this is the same

28. Plummer, H. S.: Personal communication.

as the impure sodium salt which Squibb now manufactures for oral use. Most other observers refer to the absorption of thyroxine, but an investigation of the products which they used (the thyroxine tablets of Henning, Schering and Hoffmann-La Roche) shows that they did not contain pure thyroxine but a sodium salt of thyroxine. A perusal of the data reported in this and subsequent papers will show this distinction to be of importance.

The present study has two objectives:

1. To prove definitely whether or not thyroxine is effective when administered by mouth.

2. A quantitative comparison of the effects of administering thyroxine by the oral and parenteral routes and desiccated thyroid by mouth.

METHOD

All of our observations have been made on patients with myxedema; in other words, in conditions under which all thyroid preparations are known to have their greatest effect. To exclude the possibility of variations in effect from patient to patient, the various preparations used have been compared in the same patient. We have determined the effect of various doses of Squibb's crystalline thyroxine when administered intravenously or subcutaneously; the effect of various doses of the monosodium salt of synthetic thyroxine (Hoffmann-La Roche) by mouth, and the effect of various doses of Wilson's desiccated thyroid (iodine content, 0.23 per cent) by mouth. There are also some data on the effect of oral administration of pure synthetic thyroxine and Squibb's thyroxine tablets for oral use. More data on the effect of these two substances will be reported at a later date. The pure synthetic thyroxine used for oral administration was given in the form of tablets containing 1 mg. each, which were specially prepared for us by Hoffmann-La Roche. The monosodium salt of thyroxine refers to the so-called thyroxine tablets which Hoffmann-La Roche ordinarily sell for oral administration. Each tablet contains 1.03 mg. of the monosodium salt and hence is equivalent to 1 mg. of thyroxine. The Squibb thyroxine for oral use is said by the manufacturers to be the acid-insoluble fraction after the preliminary alkaline hydrolysis in the separation of thyroxine from the thyroid gland and was used in the form of tablets containing 0.4 mg. each. Its exact composition is apparently not known. According to "New and Nonofficial Remedies," [29] it is the partially purified disodium salt of thyroxine, approximately 25 per cent admixed with the acid-insoluble humus-like products of protein hydrolysis. The tablets that we received from Squibb during the latter part of our observations were slightly darker than those we received during the first part. Whether variations in composition account for some of the variations in effect in the different patients is uncertain. Although synthetic thyroxine was used by mouth and Squibb's thyroxine intravenously, both appear to be the same thing chemically and physiologically.

The data on the first patient up to the five hundred and eighth day and on the second patient up to the four hundred and fifteenth day have been reported else-

29. New and Nonofficial Remedies, Chicago, American Medical Association, 1931.

where to illustrate another point (Thompson, McLellan, Thompson and Dickie[30]). The method of preparing the thyroxine (Squibb) for intravenous and subcutaneous injection may be seen in that report. All that seems of importance in the present paper is to state that it was put into solution for injection by adding to its suspension in distilled water 2 or 3 drops of 10 per cent sodium hydroxide.

TABLE 1.—*Effect on Basal Metabolism of the Daily Administration of Thyroxine in Various Forms and of Desiccated Thyroid in Six Patients with Myxedema*

Form	Daily Medication: Amount, Mg.	Daily Medication: Method of Administration	Basal Metabolic Rate, per Cent Normal: Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
None	....	.....	−33	−41	−34	−31	−25	−18
Squibb's crystalline thyroxine in alkaline solution	0.05	Intravenously	....	−34				
	0.10	Intravenously	−21	−25				
	0.20	Intravenously	− 7	−15				
	0.30	Intravenously	+ 1	− 8				
	0.40	Intravenously or subcutaneously	....	+ 5				
Squibb's tablets (impure sodium salt of thyroxine)	0.20	By mouth	−12	−12	−12			
	0.40	By mouth	− 4	....	− 7	− 4		
	0.60	By mouth	− 8	− 1	− 6			
Hoffmann-La Roche's tablets (monosodium salt of synthetic thyroxine)	1.03	By mouth	....	....	....	−10	+ 8	+27
	1.55	By mouth	+ 7	+ 6	+ 2	+ 6		
	2.06	By mouth	+23	+ 9	+ 5			
Hoffmann-La Roche's tablets (pure synthetic thyroxine)	1.00	By mouth	−19	−13	−24			
	2.00	By mouth	....	−12				
Wilson's desiccated thyroid	0.86 grain	By mouth	....	....	....	....	....	+ 2
	1 grain	By mouth	− 6	−16				
	1.5 grain	By mouth	+ 7	+ 1				

TABLE 2.—*Comparison of the Doses of the Various Substances Required to Hold the Basal Metabolism at the Normal Level, on the Basis of Their Iodine Contents*

Form	Iodine Content of Maintenance Dose (Mg.): Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Wilson's desiccated thyroid by mouth	0.19	0.23	....	....	....	0.12
Squibb's crystalline thyroxine intravenously in alkaline solution	0.20	0.23				
Squibb's tablets (impure sodium salt of thyroxine) by mouth	0.46	0.40	0.47	0.30		
Hoffmann-La Roche's tablets (monosodium salt of synthetic thyroxine) by mouth	0.85	0.88	0.94	0.82	0.49	0.26

There are three methods of comparing the substances used in patients with myxedema:

1. Determination of the dose that is just adequate to maintain the basal metabolism at the normal level.

30. Thompson, W. O.; McLellan, L. L.; Thompson, P. K., and Dickie, L. F. N.: The Rates of Utilization of Thyroxine and of Desiccated Thyroid in Man: Relation Between the Iodine in Desiccated Thyroid and in Thyroxine, J. Clin. Investigation **12**:235, 1933.

2. Determination of the effect on the basal metabolism of a single large dose, e.g., 10 mg. of thyroxine or its equivalent.

3. Determination of the rate at which a given dose will raise the basal metabolism to normal.

For the purposes of the present study we have selected the first method.

DATA

The data are summarized in tables 1 and 2 and recorded in detail in charts 1 to 7. The level recorded on any dose of any preparation is the average of the basal metabolisms after the rate had become stationary during the administration of the particular dose. It may be noted that the dose of any substance was rarely changed until the patient had been receiving it for several months.

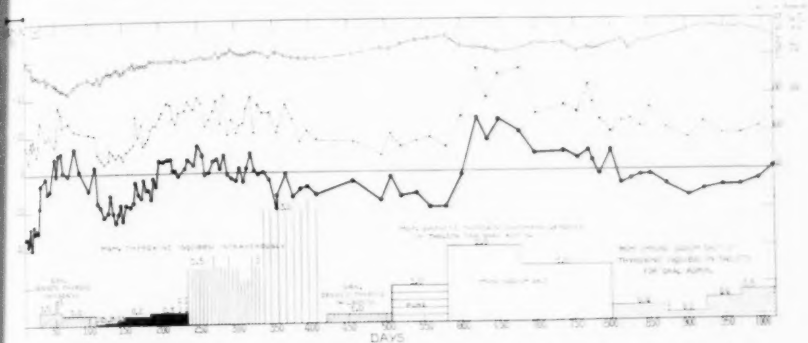

Chart 1.—Comparison of the effects of administering various forms of thyroxine by mouth, desiccated thyroid by mouth and thyroxine intravenously in a patient with myxedema (Miss M. F.; height, 161 cm.; age, 42).

In this and subsequent charts the solid black line represents the basal metabolic rate; the broken line, the pulse rate and the line of circles, the weight.

In the first patient (chart 1), whose basal metabolism was minus 33 per cent during the myxedematous state, the rate could be held at the normal level in the following ways:

1. By the daily administration of 0.3 mg. of Squibb's crystalline thyroxine intravenously (0.2 mg. of iodine).

2. By the daily administration of about 1.25 grains (81 mg.) of Wilson's desiccated thyroid (0.19 mg. of iodine). (For the calculation of this and the first figure, see a previous report by Thompson, McLellan, Thompson and Dickie.[30]).

3. By the daily oral administration of about 1.3 mg. of the monosodium salt of thyroxine (0.85 mg. of iodine). (This was calculated from the fact that 1.55 mg. daily held the basal metabolism at a level of plus 7 per cent.)

4. By the daily administration of about 0.71 mg. of Squibb's thyroxine (0.46 mg. of iodine) for oral use (calculated from the fact that 0.6 mg. daily held the basal metabolism at a level of minus 8 per cent).

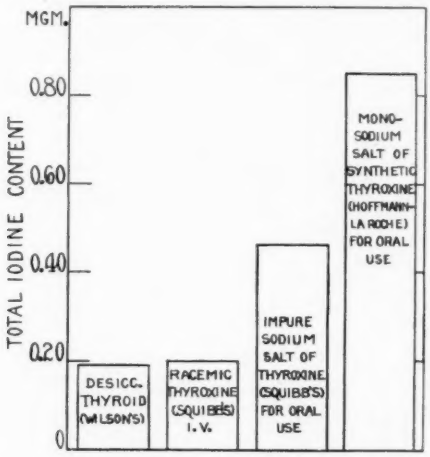

Chart 2.—Comparison of the amounts of iodine in the doses of the various substances necessary to hold the basal metabolism at the normal level in the first patient.

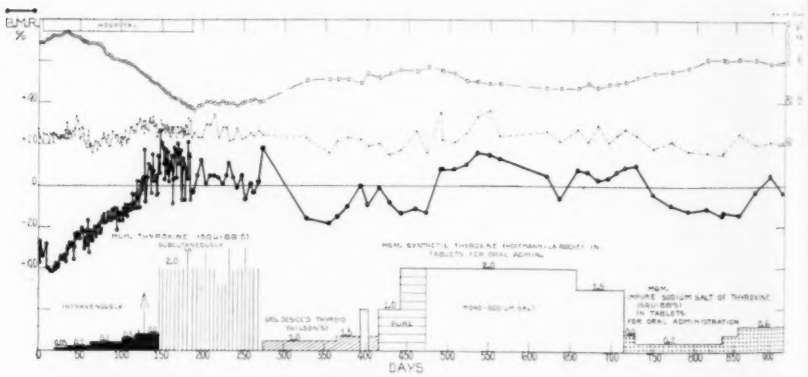

Chart 3.—Comparison of the effects of administering various forms of thyroxine by mouth, desiccated thyroid by mouth and thyroxine intravenously and subcutaneously in a patient with myxedema (Mrs. M. R.; height, 155 cm.; age, 40).

In chart 2 we have compared the daily maintenance dose of the four substances mentioned on the basis of their iodine contents.

In the second patient (chart 3), whose basal metabolism was minus 41 per cent during the myxedematous state, the rate could be held at the normal level in the following ways:

1. By the daily intravenous or subcutaneous administration of about 0.35 mg. of Squibb's crystalline thyroxine (iodine content, 0.23 mg.).

2. By the daily administration of about 1.5 grains (97 mg.) of Wilson's desiccated thyroid (0.23 mg. of iodine). (For the calculation of these first two figures, see a previous paper by Thompson, McLellan, Thompson and Dickie.[30])

3. By the daily oral administration of about 1.35 mg. of the monosodium salt of thyroxine (0.88 mg. of iodine). (This was calculated from the fact that 1.55 mg. daily held the basal metabolism at a level of plus 6 per cent.)

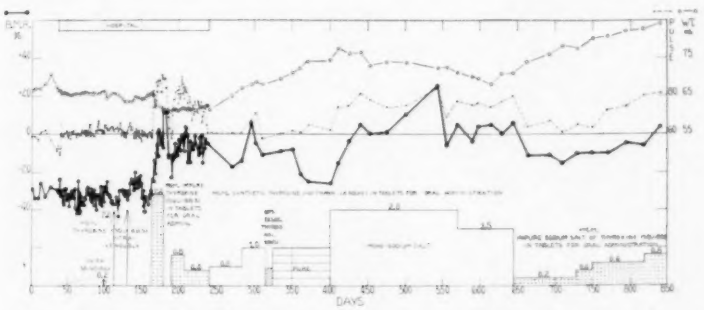

Chart 4.—Comparison of the effects of the oral administration of an impure sodium salt of thyroxine and the monosodium salt of synthetic thyroxine in a patient with myxedema (Mrs. E. R.; height, 167.5 cm.; age, 44).

4. By the daily administration of about 0.61 mg. of Squibb's thyroxine (0.4 mg. of iodine) for oral use (calculated from the fact that 0.6 mg. daily held the basal metabolism at a level of about minus 1 per cent).

In the third patient (chart 4), whose basal metabolism was minus 34 per cent during the myxedematous state, the rate could be held at the normal level in the following ways:

1. By the daily administration of about 0.73 mg. of Squibb's thyroxine (iodine content, 0.47 mg.) for oral use (calculated from the fact that 0.6 mg. daily held the basal metabolism at a level of minus 6 per cent).

2. By the daily oral administration of about 1.46 mg. of the monosodium salt of thyroxine (iodine content, 0.94 mg.). (This was calculated from the fact that 1.55 mg. held the basal metabolism at a level of plus 2 per cent.)

In the fourth patient (chart 5), whose basal metabolism was minus 31 per cent during the myxedematous state, the rate could be held at the normal level in the following ways:

1. By the daily administration of about 1.3 mg. of the monosodium salt of thyroxine (0.82 mg. of iodine), judging from the level on 1.55 mg. per day. If, however, the level to which the basal metabolism was raised by 1.03 mg. daily (minus 10 per cent) were used in the calculation, the figure for maintenance at the normal level would be raised to 1.52 mg. daily.

2. By the daily administration of about 0.46 mg. of Squibb's thyroxine (iodine content, 0.3 mg.) for oral use (calculated from the fact that 0.4 mg. daily held the metabolism at a level of minus 4 per cent).

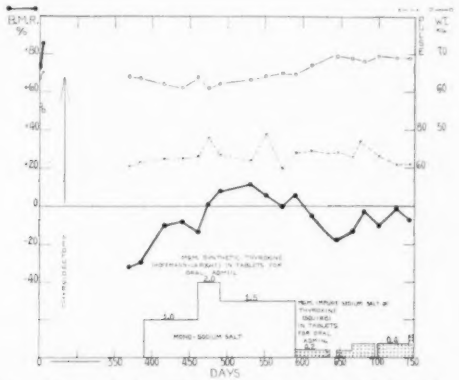

Chart 5.—Comparison of the effects of the oral administration of an impure sodium salt and the monosodium salt of synthetic thyroxine in a patient with myxedema (Miss M. T.; height, 164 cm.; age, 40).

In the fifth patient (chart 6), whose basal metabolism was minus 25 per cent during the period of myxedema, the rate could be held at the normal level by the daily administration of about 0.78 mg. of the monosodium salt (0.49 mg. of iodine), judging from the fact that 1.03 mg. daily held the basal metabolism at a level of plus 8 per cent. Data on this patient during her pregnancy have been ignored in calculating levels.

In the sixth patient (chart 7) whose basal metabolism was minus 18 per cent after the administration of desiccated thyroid had been omitted for eighty-five days, the basal metabolism could be held at the normal level in the following ways:

1. By the administration of about 0.77 grains (50 mg.) of Wilson's desiccated thyroid (0.12 mg. of iodine) daily (calculated from the fact that 0.86 grains (56 mg.) daily held the rate at plus 2 per cent).

2. By the daily administration of about 0.4 mg. (0.26 mg. of iodine) of the monosodium salt of thyroxine (calculated from the fact that 1.03 mg. daily held the metabolism at plus 27 per cent).

It may be noted that in the first and third patients the level during the administration of 1 mg. of Hoffmann-La Roche's synthetic thyroxine daily by mouth was lower than would be expected on the basis of the results with 1.5 mg. daily. Thus, in the first patient, the basal

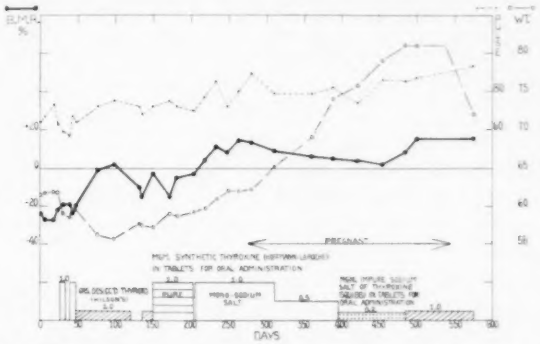

Chart 6.—Effects of the oral administration of monosodium thyroxine in a patient with myxedema (Mrs. M. S.; height, 164 cm.; age, 37).

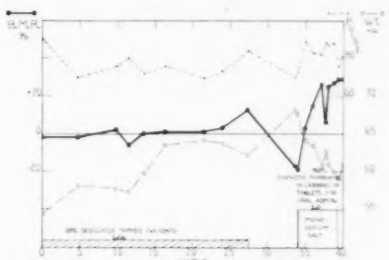

Chart 7.—Comparison of the effects of oral administration of desiccated thyroid and monosodium thyroxine in a cretin (Mr. J. K., age 20). (The height of this patient varied during the period of observation as follows: Jan. 3, 1930, 157.5 cm.; May 26, 1930, 161 cm.; Oct. 24, 1930, 165 cm.; May 16, 1931, 166 cm.; April 2, 1932, 167 cm.; Nov. 19, 1932, 167.5 cm.).

metabolism dropped to minus 19 per cent during the administration of 1 mg. daily, although it was plus 7 per cent during the administration of 1.5 mg. daily; and in the third patient, the corresponding levels were minus 24 and plus 2 per cent, respectively. In the second patient, it may be seen that during the first administration of 2 mg. of Hoffmann-La Roche's synthetic thyroxine daily by mouth, the metabolism dropped to a lower level (minus 12 per cent) than it was later

during the administration of 1.5 mg. daily (plus 6 per cent). In the fifth patient, when the administration of Hoffmann-La Roche's synthetic thyroxine by mouth was first substituted for that of Wilson's desiccated thyroid the metabolism dropped to a level of minus 10 per cent and then later it was at a level of plus 8 per cent on the same dose. We were at a loss to explain these apparent discrepancies until a careful perusal of our data showed that the results which seemed to be too low coincided with the administration of pure crystalline thyroxine in tablet form instead of its monosodium salt. From these data, it would appear that pure crystalline thyroxine may have a slight effect when given by mouth. If they were fair indications of its effect by this route, it would have taken 2.4, 2.8, 3.4 and 1.7 mg. daily, respectively, in patients 1, 2, 3 and 5 in order to hold the basal metabolism at the normal level. This is from two to two and one-half times as much as was required of the monosodium salt to accomplish the same result. However, since these data were collected we have observed that the administration of single doses of from 10 to 100 mg. of pure crystalline thyroxine by mouth or duodenum to patients with myxedema had little or no effect on the basal metabolism. In one patient with marked myxedema we have been able to raise the basal metabolism from minus 40 per cent to normal by the prolonged oral administration of pure thyroxine, first in a dose of 25 mg. daily and then in a dose of 50 mg. daily. The exact amount necessary to maintain the metabolism at the normal level in this patient is yet to be determined.

While thyroxine has much less effect when given orally in the form of its monosodium salt than when given intravenously in alkaline solution, the effect of the monosodium salt was nevertheless not spasmodic but fairly constant in the six cases observed. Thus, in patients 1, 2, 3 and 4, whose levels of basal metabolism during the period of myxedema were minus 33 per cent, minus 41 per cent, minus 34 per cent and minus 31 per cent, respectively, the daily administration of 1.55 mg. held the metabolism at levels of plus 7 per cent, plus 6 per cent, plus 2 per cent and plus 6 per cent, respectively, changes of from 36 to 47 points, or changes per milligram of from 23 to 30 points. In patients 5 and 6, whose levels of basal metabolism during the myxedematous state were minus 25 per cent and minus 18 per cent, respectively, 1.03 mg. daily by mouth held the metabolism at levels of about plus 8 per cent and plus 27 per cent, respectively, or a change per milligram of 32 points in the fifth patient and 44 points in the sixth. Thus, in all six patients the average change per milligram was 30 points, with a maximum change of 44 points and a minimum change of 23 points. Some observations which we have made recently on the effect of single large doses of the monosodium salt by mouth indicate that a greater variation in effect may occur. Thus, in one patient with myx-

edema the administration of 10.3 mg. of the monosodium salt raised the basal metabolism from minus 37 per cent to minus 22 per cent, whereas in another patient with myxedema the administration of 30.9 mg. in one dose raised the metabolism only from minus 22 per cent to minus 12 per cent.

In the first patient it may be noted that when the administration of Squibb's tablets was first substituted for that of the monosodium salt of thyroxine, a dose of 0.4 mg. per day appeared to hold the basal metabolism at a level of about minus 4 per cent for about two and one-half months, whereas later 0.6 mg. per day held the metabolism at a level of only minus 8 per cent. There are at least two possible explanations for these apparent discrepancies:

1. In patients with myxedema the basal metabolism drops slowly from the normal level on omission of medication, and a dose of thyroxine which might be inadequate for maintenance at the normal level over a long period might appear to be adequate for a short period.

2. The composition of Squibb's tablets may vary. The data on the first three patients are consistent with the first explanation. Thus, in the first patient, when the administration of 0.2 mg. daily of Squibb's thyroxine for oral use was substituted for the administration of 0.4 mg. daily for forty-nine days, the basal metabolism dropped to only minus 12 per cent. The data during the daily administration of 0.2 mg. in the second and third patients likewise show a greater response to this small dose than would be expected from the results with larger doses. Slow reduction in metabolism may also explain the fact that pure synthetic thyroxine administered by mouth appeared to have a greater effect in the first three patients and in the fifth patient than we would expect on the basis of our recent data previously referred to.

COMMENT

The main problem is why the form in which thyroxine is given by mouth determines its effect on the basal metabolism. To be more specific, the things to be explained are why it has much less effect when administered by mouth in the form of its monosodium salt than when given intravenously or subcutaneously in alkaline solution, and much less effect than when given orally in the form of desiccated thyroid or combined with a polypeptide (Salter, Lerman and Means [31]), and why pure thyroxine itself has even less effect than its monosodium salt when given by mouth. There appear to be at least three explana-

31. Salter, W. T.; Lerman, J., and Means, J. H.: The Calorigenic Action of Thyroxin Polypeptide, J. Clin. Investigation **12**:327, 1933.

tions possible: (1) the solubility of the substance administered, (2) destruction in the gastro-intestinal tract and (3) some undetermined factor.

Knipping [11] favored the second view, and said that since thyroxine has less effect when given by mouth than when given intravenously it must follow that some of it is destroyed in the gastro-intestinal tract. Barnes [32] recently obtained suggestive evidence that thyroxine may be destroyed to the extent of about 11 per cent in vitro by the action of pancreatic enzymes. We [30] have previously reported that in the first two patients of this study, about the same results were obtained with desiccated thyroid by mouth as with thyroxine intravenously on the basis of equal iodine contents, and Salter, Lerman and Means [31] showed that the effect of thyroxine polypeptide is nearly as great when given by mouth as when given intravenously. It would, therefore, seem that if any destruction of thyroxine occurs, it is not very great when the thyroxine is combined with a protein or a polypeptide. It is uncertain how far the digestion of desiccated thyroid or of thyroxine polypeptide proceeds in the small intestine and just in what form thyroxine is absorbed. Barnes, Carlson and Riskin [33] showed that, during the digestion of desiccated thyroid, no iodine compound can be precipitated from the blood with a half-saturated solution of ammonium sulphate. Harington and Salter [27] found a small amount of free thyroxine at the end of from seventy-two to ninety-six hours in the preparation of their thyroxine polypeptide by tryptic digestion of 70 Kg. of dried thyroid.

While destruction in the gastro-intestinal tract is a comparatively simple explanation, we are reasonably certain that at best it accounts for only a part of the differences in effects observed. If it were the only explanation, it would seem strange that the monosodium salt of thyroxine was less affected by intestinal enzymes than thyroxine itself. Moreover, we have just made observations which show that when thyroxine is given by mouth in alkaline solution (disodium salt), it has much more effect than when given in the form of its monosodium salt. Since thyroxine is the least soluble of the three and the disodium salt the most soluble, the solubility of the thyroxine compound administered would appear to be a factor in its absorption. It might be supposed that the alkalinity of the contents of the small intestine would cause some of the sodium salt of thyroxine to be formed. However, it is probable that if this reaction occurs at all, it affects only a small part of the thyroxine, because we have given single doses of as

32. Barnes, B. O.: Personal communication.

33. Barnes, B. O.; Carlson, A. J., and Riskin, A. M.: Studies on Thyroglobulin: I. The Digestibility of Thyroglobulin, Am. J. Physiol. **98**:86, 1931.

much as 50 mg. directly into the duodenum in patients with myxedema without demonstrable effect on the basal metabolism. Harington and Salter [27] said: "The physical properties of thyroxine are such as to make it highly probable that the absorption of this substance after oral administration would be inefficient and erratic; the digestion product, on the other hand, possessing as it does a much wider range of solubility, might well be absorbed almost quantitatively . . ." Solubility of the thyroxine compound administered would, therefore, appear to be important and destruction by intestinal enzymes must be considered; but only future work will determine whether or not some other factor, as yet unknown, also plays a rôle.

Schittenhelm and Eisler [34] made interesting observations which show that the site of absorption of thyroxine is the small intestine and that comparatively little is absorbed from the stomach. However, they used only an alkaline solution of thyroxine, and their experiments, while very instructive in themselves, do not solve the problem discussed here.

The difference in effect between the monosodium salt of thyroxine and Squibb's thyroxine for oral use is of interest. The fact that Squibb's tablets contain some disodium thyroxine may account in part for their greater action.

SUMMARY

In six patients with myxedema whose basal metabolism varied from minus 18 per cent to minus 41 per cent (average, minus 30 per cent) during the period of myxedema, it was necessary to administer from 0.40 to 1.46 mg. (average, 1.1 mg.) of the monosodium salt of thyroxine daily by mouth in order to hold the basal metabolism at the normal level. In the two patients in whom a comparison of the daily maintenance dose was made, it was noted that the effect of the monosodium salt by mouth was only from one-quarter to one-fifth as great as that of thyroxine given intravenously in alkaline solution.

Pure synthetic thyroxine had much less effect by mouth than its monosodium salt.

Squibb's thyroxine for oral use had an effect greater than that of the monosodium salt and less than that of thyroxine given intravenously in alkaline solution. Thus in four patients whose basal metabolism varied from minus 31 per cent to minus 41 per cent (average, minus 35 per cent) during the period of myxedema, it was necessary to administer from 0.46 to 0.73 mg. (average, 0.63 mg.) daily of this product in order to hold the basal metabolism at the normal level. In all four patients the effect of this substance was from two to two and

34. Schittenhelm, A., and Eisler, B.: Ueber die Resorption des Thyroxins nach oraler Zufuhr, Ztschr. f. d. ges. exper. Med. **80**:569, 1932.

one-half times as great as that of the monosodium salt by mouth, while in the two patients in whom the comparison was made, it was only about one-half as great as the effect of thyroxine given intravenously in an alkaline solution.

We have previously reported that in the first two patients of this study the effects of desiccated thyroid by mouth and thyroxine intravenously or subcutaneously were the same on the basis of equivalent iodine contents. In the digestion of desiccated thyroid, peptides and polypeptides of thyroxine are formed which have a wide range of solubility.

The solubility of thyroxine compounds appears to be a factor in their absorption from the gastro-intestinal tract and hence in their effect on the basal metabolism.

BENIGN FAMILIAL POLYCYTHEMIA

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AND
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Few instances of familial polycythemia have been reported. No thorough studies have been made of the families of patients with this condition.

Nichamin,[1] in 1907, observed a patient with mild polycythemia whose mother and sister had enlargement of the spleen and cyanosis. No studies were made on the blood of the relatives.

Bernstein,[2] in 1914, recorded what he believed to be the first published report of the familial incidence of polycythemia. The blood of the patient contained 12,500,000 red corpuscles per cubic millimeter and 140 per cent hemoglobin. There were splenomegally and cyanosis. The son of this patient did not have a palpable spleen, but his blood showed 7,500,000 red corpuscles and 120 per cent hemoglobin.

Tancré,[3] in 1917, reported the occurrence of polycythemia in two sisters, one of whom had 13,000,000, and the other 6,100,000, red blood corpuscles per cubic millimeter of blood. He suggested the possibility of familial occurrence.

Engelking,[4] in 1920, examined the members of a family in which the condition was present in three generations: in the grandmother, in the mother and in five children. In the children infantilism also was present, and in some there were disturbances of the functions of the glands of internal secretion.

Doll and Rothschild,[5] in 1922, stated that they had observed a family in which five of six children had Huntington's chorea and two of these had polycythemia.

From the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine of the Harvard Medical School.

1. Nichamin, S. B.: Ein Fall von Erythrämie, Med. Oboz., 1907, no. 6; abstr., Folia haemat. **6**:301, 1908.

2. Bernstein, J.: Three Cases of Polycythemia Rubra, West London M. J. **19**:207, 1914.

3. Tancré, E.: Zur Polycythemia rubra, Deutsches Arch. f. klin. Med. **123**:435, 1917.

4. Engelking, E.: Ueber Polyzythämie als vererbbare Störung der inneren Sekretion, Deutsche med. Wchnschr. **46**:1140, 1920.

5. Doll, H., and Rothschild, K.: Familiäres Auftreten von Polycythaemia rubra in Verbindung mit Chorea progressiva hereditaria Huntington, Klin. Wchnschr. **1**:2580, 1922.

Signorelli,[6] in 1923, observed a man with 9,200,000 red cells per cubic millimeter of blood and 155 per cent (Sahli) hemoglobin. This man's sister had an enlarged spleen and a slight increase in the number of red blood cells but a normal amount of hemoglobin.

Curschmann,[7] in 1923, stated that one of his patients with polycythemia had several relatives whose histories suggested a familial occurrence.

Owen,[8] in 1924, reported the case of a man 46 years old whose blood contained 9,700,000 red corpuscles per cubic centimeter and 120 per cent hemoglobin and whose spleen extended well below the costal margin. The mother and father of this patient had florid complexions. One brother had 6,120,000 red blood cells per cubic millimeter and 110 per cent hemoglobin. His spleen was not palpable. Three sisters had normal blood counts. In no member of this family was the leukocyte count elevated. Owen believed the disease to be familial and directly inherited.

TABLE 1.—*Findings in the Blood in Engelking's Cases*

	Age, Years	Red Blood Cells, per C.Mm.	Hemoglobin, per Cent	White Blood Cells, per C.Mm.	Hematocrit, per Cent
1. Mother	49	8,160,000	98	8,600	57
2. Son	21	11,390,000	150	9,200	84
3. Son	17	9,870,000	140	7,500	80
4. Daughter	10	12,160,000	150	9,500	76
5. Son	8	4,400,000	65	7,400	45
6. Son	5	8,010,000	140	11,400	70

Wieland,[9] in 1924, made a further report on the family studied by Engelking. He stated that it was probable that polycythemia existed in three generations, and he believed the disease to be a constitutional hereditary defect. Table 1 illustrates the findings in these cases.

Herz,[10] in 1925, studied three families in which he believed there was a tendency toward the occurrence of the disease. However in no case was the spleen enlarged, and in only one did the hemoglobin value exceed 90 per cent. In only two of the twelve members of the three families did the number of red blood cells exceed 6,800,000 per cubic

6. Signorelli, E.: Su dei casi familiari d'iperglobulia con splenomegalia e cianosi, Haematologica **4**:437, 1923.

7. Curschmann, H.: Ueber konstitutionelle und familiäre Hyperglobulie, Med. Klin. **19**:133, 1923.

8. Owen, T.: A Case of Polycythemia Vera with Special Reference to the Familial Features and Treatment with Phenylhydrazine, Bull. Johns Hopkins Hosp. **35**:258, 1924.

9. Wieland: Ueber Polycythaemia idiopathica beim Kinde, Ztschr. f. Kinderh. **38**:647, 1924.

10. Herz, O.: Polycythaemia idiopathica, Ztschr. f. Kinderh. **40**:151, 1925.

millimeter. In every case the percentage of polymorphonuclear neutrophils was normal.

Kretschmer,[11] in 1925, recorded polycythemia in three children in one family. The father was not examined, and the mother was normal. In only one of the three children was the spleen palpable. In each case there was a low white blood cell count, ranging from 4,700 to 5,400. The differential counts showed normal values for polymorphonuclear neutrophils. In two of the children the number of polymorphonuclear eosinophils was elevated to 9.6 and 5 per cent respectively. Two of the children had hemoglobin values of 140 per cent and red blood cell counts varying from 9,400,000 to 10,200,000.

Weil and Stieffel,[12] in 1926, reported polycythemia in a brother and sister. The man had a red blood cell count fluctuating between 5,500,000 and 7,000,000, whereas his sister had a count of 6,440,000. Only in the man was the spleen palpable.

Weber [13] discussed the constitutional and familial factors in primary and secondary polycythemia and recognized that a familial incidence is rare. He gave a bibliography and mentioned two instances of a familial tendency which we have not cited. There are records in the literature of at least eleven families in which polycythemia vera was thought to be familial. (There are other reports, but insufficient evidence was presented to indicate that the condition should be considered familial.) The report by Nichamin [1] was not verified by studies of the blood and it is therefore difficult to be sure that the condition was polycythemia vera. Although Signorelli's [6] case was undoubtedly one of polycythemia vera, there seems to be little justification for assuming that the patient's sister, who had a red blood cell count of 5,800,000 and 94 per cent hemoglobin, also had the disease. Curschmann [7] did not record results of examination of the blood to support his hypothesis of familial incidence. The brother of Owen's [8] patient cannot be considered, on the evidence presented, to have had polycythemia vera. His red blood cell count, although high, was within normal limits, and the spleen was not enlarged. Herz [10] did not present conclusive evidence that he was dealing with polycythemia vera or that the condition was familial.

If one judges the reported cases from a critical point of view, it appears that in only six instances (those reported by Bernstein, Tancré, Engelking and Wieland, Doll and Rothschild, Kretschmer, and Weil

11. Kretschmer, M.: Ueber familiäre, idiopathische Polycythämie im Kindesalter, Ztschr. f. Kinderh. **40**:225, 1925.

12. Weil, E., and Stieffel, R.: Deux cas de pléthore polyglobulique familiale, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1248, 1926.

13. Weber, F. P.: The Constitutional and Familial Factor in Primary and Secondary Polycythemia Rubra, M. Press **124**:128, 1927.

and Stieffel) has polycythemia with splenomegaly been conclusively shown to be a familial trait.

We had the opportunity of studying a family of ten members in which polycythemia was shown to exist in seven. The studies included, for each member of the family, at least seven determinations, over a period of one year, of red blood cell, white blood cell and hemoglobin values, together with differential leukocyte counts, enumeration of reticulocytes and measurement of the hematocrit percentage. The blood cell counts were made with pipets and counting chambers certified by the United States Bureau of Standards. Detailed histories were taken, and physical examinations, examinations of the urine, complement-fixation tests on the blood serum, quantitive measurements of the bilirubin and icterus index and study of the gastric secretions were made.

REPORT OF A CASE

The first member of the family studied (case 3, tables 2, 3 and 4) was a 24 year old white unmarried Italian student who presented strikingly few complaints. Accidentally he was found to have an elevated red blood cell count, averaging 7,800,000. He had moderately severe headache two or three times a week.

History.—The patient was born in Italy; at the age of 5 years he emigrated to the state of New York, where he had lived with the other members of his family for nineteen years before we saw him. Except for headaches and a few minor illnesses he had been perfectly well. As a child he had measles, mumps, influenza and tonsillitis. Twelve years before we saw him his tonsils and adenoids were removed. During the past year a deviated nasal septum had been operated on. No undue bleeding or other complications followed these operations.

He had never had diphtheria, scarlet fever, smallpox, rheumatic fever, malaria, chorea, typhoid fever, pneumonia, pleurisy, tuberculosis or any other severe illness. A review of his past history as regards the various organs and systems of the body revealed no significant information. There had been no loss or gain in weight during the past two years.

The patient had had recurrent headaches since early childhood. They were characterized by dull pain, usually over the temporal region, on either the right or the left side, but more frequently on the left. The headaches did not occur at regular intervals. They persisted for a few hours and were relieved by sleep and sometimes by eating or by cold applications to the head. Their occurrence was not related to eye-strain, to constipation or to infections of the upper respiratory tract. They were not brought on by overactivity or by any other factors within his knowledge. He stated that his color had always been ruddy. He perspired freely, particularly over the forehead and the palms. He had noticed occasional tinnitus during the past few years.

Family History.—The patient was the oldest child in a family of ten. His father, aged 51, his mother, aged 50, and seven younger brothers and sisters were all living and well. There was no family history of tuberculosis, diabetes, cancer, hemorrhagic disorders, heart disease, disease of the kidneys, arthritis or anemia. The father and the paternal grandfather had florid complexions. The mother, a younger brother and a maternal aunt had headaches similar to those of the patient.

Physical Examination.—The patient was well developed, well nourished and alert and was carrying on his activities as a student without apparent discomfort. The conjunctivae and other mucous membranes were somewhat more highly colored than is normal. There were slight enlargement and moderate injection of adenoid tissue in the region of the left tonsil. The heart and lungs were normal. The blood pressure was 114 systolic and 74 diastolic. The abdomen was normal except for a palpable spleen, which was firm and not tender. On quiet respiration

TABLE 2.—*Red Blood Cells, White Blood Cells and Hemoglobin Determinations on Members of the Patient's Family* *

Cases	Age, Years								Average
1. Father.....	52	7,230,000	7,200,000	6,890,000	6,860,000	6,590,000	6,910,000	6,730,000	6,910,000
		7,650	8,200	6,725	11,950	7,850	8,150	6,650	8,167
			15.76	14.88	15.29	15.76	14.20	13.60	14.91
2. Mother.....	51	6,350,000	5,520,000	6,450,000	5,480,000	6,220,000	5,440,000	5,490,000	5,920,000
		6,400	7,750	7,500	7,000	6,475	6,550	.....	6,954
			14.82	14.66	14.35	14.51	14.51	14.74	14.59
3. Son (patient)	24	8,000,000	7,980,000	8,390,000	7,670,000	7,050,000	8,050,000	7,500,000	7,800,000
		7,600	5,900	6,940	6,750	11,150	10,050	11,500	8,555
			15.76	16.07	15.76	15.99	15.76	14.35	15.61
4. Daughter....	22	7,450,000	7,210,000	7,230,000	7,410,000	6,270,000	7,080,000	7,110,000	7,100,000
		8,000	6,750	8,050	6,150	6,400	5,450	7,700	7,014
			12.32	12.79	12.48	12.64	13.26	12.79	12.71
5. Son.....	18	7,750,000	7,650,000	7,260,000	6,950,000	6,920,000	6,770,000	7,700,000	7,280,000
		6,750	7,600	9,400	7,750	13,050	9,500	8,050	8,871
				14.04	13.42	14.35	14.51	14.35	14.13
6. Daughter....	16	5,140,000	4,490,000	4,880,000	5,210,000	4,820,000	5,160,000	4,960,000	4,900,000
		8,600	6,000	6,500	7,450	8,000	7,100	.....	7,275
			12.17	12.10	12.48	12.79	11.70	12.79	12.34
7. Daughter....	13	6,560,000	5,620,000	5,960,000	6,180,000	5,900,000	5,890,000	5,760,000	5,980,000
		6,800	9,850	11,625	17,050	15,500	10,500	8,700	11,439
			13.26	13.57	13.26	14.35	13.88	15.29	13.93
8. Son.....	10	6,700,000	6,700,000	6,750,000	6,620,000	6,320,000	7,250,000	7,220,000	6,790,000
		6,400	8,000	8,550	10,850	9,150	6,700	7,100	8,071
				11.70	12.87	13.26	12.17	12.48	12.50
9. Daughter....	9	5,510,000	4,850,000	5,540,000	4,780,000	5,350,000	5,570,000	5,064,000	5,240,000
		6,800	9,050	8,450	11,300	7,950	8,550	6,000	8,300
			13.10	13.18	12.48	13.26	12.79	12.79	12.96
10. Daughter....	11	5,270,000	5,630,000	4,960,000	5,000,000	5,320,000	5,440,000	4,730,000	5,190,000
		10,400	7,700	6,800	9,750	6,100	7,600	9,850	8,314
		13.26	13.10	13.25	12.95	13.42	14.04	12.64	13.24

* Results of six observations on each person, the first in 1931, and the last five in the period from April to July, 1932. For each patient, the upper line of figures indicates red blood cells; the middle line, white blood cells, and the lower line, the hemoglobin (Gm. per 100 cc.).

it extended 4 cm. below the costal margin in the midclavicular line. The edge of the liver could not be felt, but by percussion it was recognized to be at the costal margin.

Ophthalmoscopic examination revealed no abnormalities except that the retinal veins were possibly a little fuller and darker than is normal.

Laboratory Examination.—The results of study of the blood, of the gastric secretions and of the basal metabolic rate are recorded in tables 2 and 3.

The urine was cloudy and amber colored and had a specific gravity of 1.020. It gave negative results when tested for albumin, sugar, diacetic acid, acetone and bile. The sediment showed occasional white blood cells and no casts or red blood cells.

TABLE 3.—*Differential Leukocyte and Reticulocyte Counts, Gastric Analysis, Basal Metabolic Rate and Physical Signs in Members of the Patient's Family*

Cases	Age, Years	Reticulocytes, per Cent	Platelets	Differential Leukocyte Count					Basal Metabolic Rate	Blood Pressure	Significant Physical Signs	Gastric Analysis 20 to 40 Minutes After Alcohol Meal	
				Polymorphonuclears			Monocytes, per Cent	Lymphocytes, per Cent				Free Hydrochloric Acid, Degrees	Total Acid, Degrees
				Neutrophils, per Cent	Basophils, per Cent	Eosinophils, per Cent							
1. Father.....	52	2.4	Normal	62.5	...	2.0	7.5	28	+ 1 + 3.5	120/85	Very red face and hands; retinal vessels full and dark	10	68
2. Mother.....	51	1.6	Normal	66.5	0.5	1.0	4.0	28	+ 7.3 +12.4	112/76	Moderately red face	No analysis made	
3. Son(patient)	24	...	Moderately increased	63	...	4	12	21	— 0.9 — 4.0 — 6.0	114/74	Spleen 4 cm. below costal margin	44	51
4. Daughter...	22	2.2	Moderately increased	63.5	1.5	1.5	2.5	31	+ 2.3 + 0.6	114/70	Spleen 3 cm. below costal margin; liver 1 cm. below costal margin	18	80
5. Son.....	18	1.0	Normal	57	2.0	4.0	16	21	+13.1 +15.0	122/76	Spleen 1.5 cm. below costal margin	93	104
6. Daughter...	16	0.6	Normal	58	1.5	3.0	6.5	31	+ 9.7 +12.8	126/90	None	No analysis made	
7. Daughter...	13	1.2	Moderately increased	56	3.0	2.5	8	30.5	+ 3.3 + 2.2	124/65	Spleen 1.5 cm. below costal margin; retinal vessels full and dark	30	39
8. Son.....	10	2.4	Moderately increased	64	1.0	3.0	10	22.0	—11.5 — 8.3	110/74	Retinal veins dark	33	50
9. Daughter...	9	0.2	Normal	50	1.5	4.0	3.5	41.0	+10.7 + 4.9	96/64	Spleen 1 cm. below costal margin; retinal veins dark	No analysis made	
10. Daughter...	11	1.4	Slightly diminished	64	2.0	1.0	8	25.0	— 7.4 — 4.8	94/50	None	44	55

The icterus index of the blood serum was 10. The bilirubin content was less than 1 mg. per hundred cubic centimeter of serum. Hemolysis began in a 0.46 per cent solution of sodium chloride and was complete in a 0.22 per cent solution.

The Wassermann reaction of the blood was negative.

The bleeding time was two and a half minutes.

Summary.—The patient presented a history of frequently recurring headaches, occasional tinnitus and excessive perspiration of the palms and the face. The physical findings of importance were redness of the mucous membranes, slightly dilated and darkened retinal vessels and an enlarged spleen. The laboratory findings showed a distinctly elevated red blood cell count and a hematocrit value greater than normal.

SIGNIFICANT FINDINGS IN OTHER MEMBERS OF FAMILY

Paternal Grandfather.—The paternal grandfather, aged 103, was living and well. He had always had a very red face. He was not available for examination.

Paternal Grandmother.—The paternal grandmother died of hemiplegia at the age of 96.

Maternal Grandfather.—The maternal grandfather died of "liver trouble" at the age of 50.

Maternal Grandmother.—The maternal grandmother died of "heart trouble" at the age of 67.

Father (case 1).—The father's history and the results of examination were not remarkable except for the presence of extreme redness of the face and hands for many years, slightly enlarged and dark retinal vessels, a persistently high red blood cell count, averaging 6,910,000, and a hematocrit value of 50.3 per cent. The spleen and liver were not palpable. The heart and lungs were normal.

Mother (case 2).—The mother, aged 51, as a girl had been given the nickname "Reddie" because of the intense redness of the face, which had persisted. For twenty-five years she had frequently had bilateral headaches. A sister and her two sons had similar headaches. The results of examination were not remarkable except for a red blood cell count averaging about 5,920,000. The hematocrit value was perhaps slightly elevated, the value being 46.7 per cent. The heart and lungs were normal. The spleen and liver were not palpable.

Sister, Aged 22 (case 4).—There were no significant data in the history. Examination revealed an enlarged spleen extending on quiet respiration to 3 cm. below the costal margin in the midclavicular line. It was firm and not tender. The liver extended 1 cm. below the costal margin. The red blood cells averaged 7,100,000, and the hematocrit value was 49.5 per cent. The heart and lungs were essentially normal.

Brother, Aged 18 (case 5).—There was a history of occasional attacks of giddiness. The youth had a "pounding" sensation in the head as a result of exertion. He had recurrent unilateral headaches. Examination showed the mucous membranes and the exposed areas of skin to be more deeply colored than is normal. The retinal vessels were somewhat dilated and dark. The spleen was felt 1.5 cm. below the costal margin in the anterior axillary line; it was firm and not tender. The liver was at the costal margin. The heart and lungs were essentially normal. There was an increased amount of free hydrochloric acid in the gastric contents. The red blood cell count and the hematocrit value were distinctly elevated, being 7,280,000 and 57 per cent respectively.

Sister, Aged 16 (case 6).—The history was not significant. Examination gave essentially normal results. The blood cell count was not elevated. The spleen was not palpable.

Sister, Aged 13 (case 7).—The history was not remarkable. Examination showed moderate injection of the conjunctivae together with dilatation and darkness of the retinal veins. The spleen, which was firm and not tender, extended 1.5 cm. below the costal margin in the anterior axillary line. The liver was at the costal margin and slightly tender. The red blood cell count averaged 5,980,000, and the hematocrit reading was 46.9 per cent. The leukocyte count fluctuated from 6,800 to 17,050, the average being 11,440.

Brother, Aged 10 (case 8).—The history was not significant. The results of physical examination were essentially normal. The hematocrit value was normal, but the red blood cell count was elevated, averaging 6,790,000.

Sister, Aged 9 (case 9).—The history was not significant. The retinal veins were dark. The heart and lungs were normal. The spleen was definitely firm and not tender; it was felt 1 cm. below the costal margin. The liver was not palpable. The hematocrit value was normal. The red blood cell count was within normal limits.

Sister, Aged 11 (case 10).—The history and the results of physical examination were essentially normal. The spleen and liver were not enlarged. The red blood cell count was normal.

ADDITIONAL DATA CONCERNING THE CASES REPORTED

The history does not show that any member of the family had typhoid, malaria or any other disease commonly associated with enlargement of the spleen. For none was there a history suggesting familial jaundice. The reticulocytes did not exceed 2.4 per cent in any case. The icterus index did not exceed 10 in any case, and in only one (case 3) did the value exceed 5. The bilirubin was uniformly below 1 mg. per hundred cubic centimeters of blood serum. The Wassermann test of the blood serum was negative in each instance. In nine of the cases the blood belonged to iso-agglutination group IV (Moss classification), and in case 6 the blood was not grouped. In only one case (case 7) was the number of white blood cells abnormal. In no case was the differential leukocyte count markedly abnormal. The relative numbers of polymorphonuclear neutrophils and eosinophils were not increased above normal values. All of the members of the family were vegetarians, caring little for and only occasionally eating meat. Aside from this, their dietary history was not remarkable.

COMMENT

With reference to the existence of polycythemia and enlargement of the spleen, the members of this family may be classed in four groups, as presenting:

(*A*) Polycythemia with enlargement of the spleen: four cases (3, 4, 5 and 6).
(*B*) Polycythemia without enlargement of the spleen: three cases (1, 2 and 8).
(*C*) No polycythemia but enlargement of the spleen: one (case 9).
(*D*) No polycythemia on enlargement of the spleen: two cases (6 and 10).

Although the spleen was not felt in the father and mother (cases 1 and 2), this does not necessarily indicate that it was not or had not been enlarged. Both of these persons were short and somewhat obese, which made abdominal palpation more difficult than in the younger members of the family. Neither can we be certain that in the persons in groups C and D there were no potential possibilities of the development of polycythemia. Case 9, in which there was no polycythemia but in which the spleen was palpable, suggests this.

The fact that all of the members of the family were almost exclusively vegetarians may be of significance. If antianemic sub-

TABLE 4.—*Hematocrit Reading, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin and Mean Corpuscular Hemoglobin Concentration in Members of the Patient's Family*

Case	Age, Years	Red Blood Cells, per C.Mm.	Hemoglobin, Gm. per 100 Cc.	Hematocrit, per Cent	Mean Corpuscular Volume, Cubic Microns	Mean Corpuscular Hemoglobin, Micromicrograms	Mean Corpuscular Hemoglobin Concentration, per Cent
1. Father.....	52	6,780,000	13.57	50.30	74.2	20.0	27.0
2. Mother.....	51	5,450,000	14.59	46.66	85.6	26.8	31.3
3. Son (patient)	24	7,980,000	15.75	50.08	62.8	19.7	31.4
4. Daughter.....	22	7,110,000	12.71	49.55	69.7	17.9	25.7
5. Son.....	18	8,070,000	14.51	57.00	70.6	18.0	25.5
6. Daughter.....	16	.....	.....	.....	....	....	....
7. Daughter.....	13	5,620,000	15.37	46.93	83.5	27.3	32.8
8. Son.....	10	6,430,000	12.48	42.57	66.2	19.4	29.3
9. Daughter.....	9	5,200,000	12.79	39.60	76.2	24.6	32.3
10. Daughter.....	11	4,880,000	12.48	45.18	92.6	25.6	27.6
Normal* (10 men).....		5,000,000	14.82	46.0	92.0	29.8	32.4
Normal (10 women).....		4,600,000	13.10	42.8	93.0	28.5	31.0

* As determined in this laboratory. See Heath, C. W.: New England J. Med. **209**: 173 (July 27) 1933.

stances such as liver or iron had been administered, the condition might have been exaggerated, as the color index and the mean corpuscular hemoglobin concentration in all of the cases were distinctly low. The mean corpuscular volume was also below the lower limits of normal in five cases, and the mean corpuscular hemoglobin was decreased in seven of the nine cases in which these measurements were made (table 4).

It is of interest that all of the male members of the family (cases 1, 3, 5 and 8) and half of the female members (cases 2, 4 and 7) had polycythemia.

We were not able to study any of the more distant relatives because of their residence in Europe. Therefore, we are unable to say with certainty that other members were affected. The history, however, suggests that the paternal grandfather may have had the condition.

The cases recorded by Doll and Rothschild [5] and those studied by Engelking [4] and Wieland,[9] in which the polycythemia was associated with another inherited or familial trait (in one group, hereditary chorea, and in the other, infantilism) suggest that a defect in the germ plasm may play a part in the pathogenesis of the condition. No such associated defects were observed in our cases, with the possible exception of headache, which was present in the mother and two of her sons (cases 2, 3 and 5) and in the mother's sister.

Although there seems to be no doubt that polycythemia, together with enlargement of the spleen, was a familial trait in these cases, certain characteristic features ordinarily associated with polycythemia vera were absent. The benign course of the condition, which had undoubtedly existed for many years, the absence of leukocytosis, the normal numbers of polymorphonuclear neutrophils and eosinophils, the uniformly normal hemoglobin values and the normal basal metabolic rates speak against the diagnosis of typical polycythemia vera. It seems necessary to assume either that the members of this family had an unusual form of polycythemia vera, or, as seems more probable to us, that they presented a benign condition for which we suggest the name "benign familial polycythemia."

SUMMARY

1. A critical review of the reported examples of familial polycythemia has been presented.

2. Observations on the blood, together with other clinical studies, of ten members (two generations) of a family in which polycythemia and splenomegaly were present are reported. The existence of polycythemia in an earlier generation of the family is suggested by the history.

3. This family differed from those previously described in that characteristics of polycythemia vera, other than the increased number of red blood corpuscles and enlargement of the spleen, were not present.

4. The term "benign familial polycythemia" is suggested to distinguish this condition from polycythemia vera and from polycythemia due to recognized causes.

TEMPERATURE OF THE GASTRO-INTESTINAL TRACT

THE EFFECT THEREON OF HOT AND COLD FOODS AND OF PHYSICAL THERAPEUTIC AGENTS

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PHILADELPHIA

A wide difference of opinion exists among surgeons and internists concerning the value and action of the ice bag and the different forms of heat, applied locally, in the treatment of acute appendicitis, ulcer of the stomach or duodenum and other pathologic processes within the abdomen. In many patients, gastro-enteric upsets occur after the ingestion of ice cream, ices and iced drinks. This research, therefore, was undertaken in order to ascertain the influence exerted on gastro-intestinal temperatures by (*a*) the ingestion of hot and cold foods and drinks, and by (*b*) the local application of cold and of various forms of heat.

Eichler and Schemel [1] measured gastric temperature by means of the "fever registration apparatus" of Siemens and Halske. Their results showed that the normal gastric temperature lies between 98.6 and 99.2 F. This temperature was increased slightly by the application of the steam jet or by local irradiation with an arc light, and was decreased slightly by epigastric application of the apparatus of Winternitz, an ice bag or a trunk pack. The maximum period of application was 30 minutes; the greatest change in gastric temperature, 1.6 F.

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1. Eichler and Schemel: Ueber die Beeinflussung der Magentemperatur durch verschiedene hydrotherapeutische Applikationen und ihre Messung mit dem "Fieberregistrierapparat" nach Siemens u. Halske, Deutsche med. Wchnschr. **37**: 2371, 1911.

Bergeim [2] introduced a thermocouple of copper and iron-constantan into the stomach in the tip of a Rehfuss tube, and then measured gastric temperatures. He reported that "after the ingestion of cold foods or liquids of any kind, a half hour or more may be required to reach body temperature."

Stengel and Hopkins [3] used a similar thermocouple placed in the tip of an Einhorn tube, and determined its position in the stomach by means of a fluoroscope. Their results on 5 subjects showed the temperature of both the fundus and the pylorus to lie between 98.4 and 100.4 F. They also studied the influence on gastric temperature of ingested ice water and of hot and cold foods when included in a meal. Application of ice bags to the epigastrium for 45 minutes decreased the gastric temperature by from 1.6 to 1.8 F. Hot water bags, under the same conditions, had a practically negligible effect.

Sheard [4] described a copper-constantan thermocouple, and mentioned its use for measurement of gastric temperature.

TECHNIC

In these studies, use was made of a resistance thermometer of insulated nickel wire mounted in a silver tube 1 inch (2.5 cm.) in length and ¼ inch (0.63 cm.) in outside diameter. This thermometer was attached to a resistance thermometer recorder by means of insulated copper wires contained in a flexible rubber tube approximately ¼ inch in external diameter. The recorder had a temperature range from —10 to 120 F., and would record any temperature to which the gastro-intestinal tract might be subjected. The greatest possible error of the instrument was ±0.6 F. over its entire range, and ±0.2 F. within the range of from 90 to 110 F.; it was sensitive to a change of 0.1 F. The ruled paper passed through the recorder at the rate of 6 inches (15.24 cm.) per hour. It was graduated in increments of 1 F., and the position of the graph was interpolated to 0.1 F. The recorder was a stock article, and the thermometer was especially constructed for this research; both were manufactured by the Leeds and Northrup Company.

The thermometer and that portion of the rubber tube which was swallowed were sterilized by immersion at room temperature in a solution of hexylresorcinol S. T. 37. They were washed with sterile water just before being swallowed, since subjects complained of the prolonged action of the glycerol in the hexylresorcinol solution on the lips and pharynx when the tube was kept in the alimentary tract for an hour or longer.

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2. Bergeim, O.: Gastric Response to Foods: I. The Determination and Significance of Intragastric Conductance, Am. J. Physiol. **45**:1, 1917.

3. Stengel, A., and Hopkins, A. H.: A New Method for Determining the Intragastric Temperature in Man, with Some Observations on Its Variations After Ingestion of Hot and Cold Liquids and During Digestion, Am. J. M. Sc. **153**:101, 1917.

4. Sheard, C.: An Instrument and a Method for Measuring Intramural, Intravenous, Superficial and Cavity Temperatures, Am. J. Clin. Path. **1**:209, 1931.

For measurement of the gastric temperature, the thermometer was introduced in the same manner as a stomach tube. For measurement of the temperature of the upper part of the intestine, the thermometer was introduced in the same manner as a duodenal tube for nonsurgical biliary drainage. In order to protect the tube from abrasion, the portion between the teeth was surrounded by a loosely fitting piece of soft rubber tubing. For measurement of the temperature of the sigmoid, the thermometer was introduced through a sigmoidoscope well past the sphincter of O'Beirne, the subject being in either the Sims or the knee-chest position. The wall of the sigmoid was then permitted to collapse about the thermometer. Oral temperature was measured with a clinical thermometer.

Fig. 1.—Roentgenogram showing meal of barium sulphate in the stomach and a thermometer in the jejunum.

The subjects were chiefly technicians and students in the schools of medicine and nursing. They were all healthy and active. In all the experiments except those on the sigmoid, the subject had an empty stomach.

In the experiments with ice water, ice cream and coffee, the subjects were in a sitting position; they were requested to ingest these substances as rapidly as possible without discomfort, and the time required for ingestion was measured with a stopwatch. In all the other experiments on the stomach and the upper part of the intestine, the subjects were in a supine position.

In experiments concerning the influence of physical therapeutic agents on the gastric temperature, the actual position of the stomach was determined by roentgenography. One or more days prior to the actual experiment, a one cent coin was fastened over the umbilicus; a test meal of barium sulphate was given on an

empty stomach. Fluoroscopy was performed; roentgenographs of the stomach were taken in the usual manner, with the patient prone and supine. The position of the stomach with respect to both the umbilicus and the bony landmarks was thereby ascertained. During the actual experiment, the agent was applied directly over the true epigastric region.

In measurement of the temperature of the upper part of the intestine, and in study of the influence of physical therapeutic agents on that temperature, the following technic was found most satisfactory for determining the position of the thermometer in the intestine: One or more days prior to the actual experiment, roentgenographs of the stomach were taken as described, with the patient both prone and supine. On the day of the actual experiment, after the thermometer had been passed to the 75 cm. mark, roentgenographs were taken, with the patient both prone and supine, usually with a one cent coin fastened over the umbilicus, and the films were developed immediately. By comparison of the pictures taken with the patient in the prone position, it was possible to determine whether the thermometer had passed into the intestine, and if it had, the region it had reached (duodenum or jejunum). If the thermometer had not left the stomach, the tube was drawn up to the 55 cm. mark and then reswallowed, in the usual manner, to the 75 cm. mark; another set of roentgenographs was then taken. The pictures with the patient in the supine position were used to determine the exact region of the body surface on which to apply the physical therapeutic agent so that the thermometer lay in the center of the area of action.

All temperatures are reported on the Fahrenheit scale.

TEMPERATURE OF THE GASTRO-INTESTINAL TRACT

Gastric temperature was taken as recorded on the graph as soon as the recorder had come to equilibrium after the thermometer had been swallowed. In 129 men, the maximum gastric temperature was 101.8 F., the minimum 97.8 and the average 99.2. In 128 women, the maximum was 102.2 F., the minimum 97.5, and the average 99.4. In table 1, the subjects have been classified according to their gastric temperature in groups, each with a range of 1 F. With each sex, the gastric temperature was between 99 and 99.9 F. in approximately six tenths of the subjects, and between 98 and 100.9 F. in over nine tenths of the subjects.

Comparison of Gastric with Oral Temperature.—In 124 of the men and all of the women, the temperatures of both the stomach and the mouth were taken. In both sexes, the gastric temperature usually was higher than the oral temperature, the average difference being 0.9 F. in the men and 1.25 F. in the women. In individual men, the gastric temperature was as much as 0.8 F. lower and as much as 3.1 F. higher than the oral temperature. In individual women, the gastric temperature was as much as 0.6 F. lower and as much as 4.4 F. higher than the oral temperature. In table 2, the subjects have been divided according to the magnitude of the deviation of the gastric temperature from the oral temperature, each group having a range of 1 F. The percentage of the subjects falling into each group is shown.

Variation in Gastric Temperature.—The gastric temperature of a subject may vary during a comparatively short period of time. In the forty experiments summarized here, the variation was taken as the difference between the highest and the lowest temperatures recorded on the graph while the thermometer was in the subject's stomach. In 15 men, the experiments extended over periods of time ranging from 0.5 to 3.5 hours; variations as great as 3.8 F. were noted. In 25 women, each experiment occupied from 0.75 to 2 hours. Variations as great as 1.3 F. were observed. With both sexes, some subjects showed no variation, the graph demonstrating that no change in temperature occurred.

Temperature of the Upper Part of the Intestine.—The intestinal temperature was taken as recorded on the graph after the roentgenograph had demonstrated the thermometer to be in the upper part of the intestine. Measurements were made on 34 men (33 duodenal and 1 jejunal measurement) and 19 women (16 duodenal and 3 jejunal measurements).

TABLE 1.—*Gastric Temperature*

Temperature, F.	Men	Women
97- 97.9	3	1
98- 98.9	28	21
99- 99.9	76	77
100-100.9	20	21
101-101.9	2	7
102-102.9	0	1

TABLE 2.—*Deviation of Gastric Temperature from Oral Temperature*

Deviation, F.	Men, per Cent	Women, per Cent
−0.1 to −0.9	8.06	3.13
0	4.84	2.34
0.1 to 0.9	40.32	35.16
1.0 to 1.9	36.29	41.41
2.0 to 2.9	9.68	14.06
3.0 to 3.9	0.51	3.13
4.0 to 4.9	0	0.78

In the men, the intestinal temperature ranged between 98 and 100.1 F., with an average of 99.1 F. The intestinal temperature was exactly the same as the gastric in 12 cases, higher than the gastric temperature in 11 cases and lower than the gastric temperature in 11 cases. The maximum difference between the temperature of the two organs was 0.4 F.; the average difference, less than 0.1 F.

In the women, the intestinal temperature ranged between 98 and 99.9 F., with an average of 98.9 F. The intestinal temperature was exactly the same as the gastric temperature in 5 cases, higher than the gastric temperature in 6 cases and lower than the gastric temperature in 8 cases. The maximum difference between the temperatures of the two organs was 0.9 F.; the average difference, less than 0.1 F.

Sigmoidal Temperature.—The sigmoidal temperature was taken as that recorded on the graph as soon as the recorder had come to equilibrium after the thermometer had passed through the sphincter of O'Beirne. In 6 normal subjects (3 men and 3 women), the average temperature of the sigmoid was 101.2 F., the maximum 101.5 and the minimum 100.8. The sigmoidal temperature was always higher than the oral temperature, on the average by 2.9 F.; the least difference between the two temperatures was 2 F.; the greatest difference, 3.5 F.

INFLUENCE OF HOT AND COLD FOODS ON GASTRIC TEMPERATURE

Ice Water.—The subjects included 27 men and 25 women. Each subject drank 250 cc. of ice water, the temperature of which was measured by means of a mercury thermometer immediately prior to ingestion. An immediate, marked decrease in gastric temperature resulted; this was followed by a rise, at first quite rapid, then progressively slower; finally the curved graph again became a straight line which recorded exactly the same temperature for at least 10 minutes. This constant temperature was taken as the final temperature or temperature after recovery; it was approximately the same as the initial temperature, but tended to be a few tenths of a degree lower than the latter. Thus, with each sex, the average of the final temperatures was 0.2 F. lower than the average of the initial temperatures. The time measured on the graph from the drop in temperature on ingestion of the ice water to the beginning of the constant final temperature was the recovery time. The results of these experiments are summarized in table 3.

The decrease in gastric temperature and the recovery time apparently did not depend on either the temperature of the ice water or the time required for its ingestion. Each of two women ingested the coldest ice water used in the experiments with their sex (temperature, 32.9 F.) in exactly the same time (0.34 minute); they yielded, respectively, the maximum and the minimum decrease in gastric temperature (42.5 and 7.2 F.); the subject with the maximum decrease had a recovery time of 31.3 minutes, while the subject with the minimum decrease had a recovery time of 65.1 minutes, the longest recovery time in the entire group of fifty-two experiments.

Ice Cream.—The subjects were 26 men and 25 women. Each subject ate 90 Gm. of ice cream, that quantity being the standard hospital portion. The temperature of the ice cream was measured by means of a mercury thermometer immediately prior to ingestion. The graph obtained was somewhat similar to that yielded by the ingestion of ice water, except that the initial decrease in temperature was less marked. As with ice water, the final temperature of the stomach was approxi-

mately the same as its initial temperature, but tended to be a few tenths of a degree lower than the latter; with each sex, the average difference between initial and final temperature was 0.2 F.

With 12 men and 4 women, the decrease in gastric temperature on the ingestion of ice cream did not exceed the maximum variation in gastric temperature previously reported for their respective sexes. However, their graphs showed the typical response to a cold stimulus, i. e., an immediate decrease in gastric temperature on eating the ice cream followed by a slow return to approximately the initial gastric temperature. Therefore, these experiments have been included in the series which is also summarized in table 3.

TABLE 3.—*Effect of Ice Water and Ice Cream on the Gastric Temperature*

Substance ingested	Observation	Sex	Maximum	Minimum	Average
Ice water	Temperature of ingested ice water, F.	Male	40.1	32.5	34.0
		Female	34.7	32.9	33.4
	Ingestion time, minutes	Male	1.12	0.11	0.33
		Female	1.35	0.21	0.59
	Decrease in gastric temperature, F.	Male	37.9	9.8	27.6
		Female	42.5	7.2	22.9
	Recovery time, minutes	Male	62.0	10.2	38.1
		Female	65.1	25.6	39.8
Ice cream	Temperature of ingested ice cream, F.	Male	23.0	—0.4	9.5
		Female	27.5	—0.4	7.7
	Ingestion time, minutes	Male	6.02	1.50	3.24
		Female	8.50	1.96	4.30
	Decrease in gastric temperature, F.	Male	43.8	1.0	8.3
		Female	14.9	0.2	5.1
	Recovery time, minutes	Male	52.8	11.5	32.6
		Female	57.0	20.0	36.1

The magnitude of the decrease in gastric temperature apparently depends on the temperature of the ice cream, the time taken for its ingestion and the subject, as may be seen from the following experiments, which are included in the series.

The apparent influence of the time taken in eating is shown by the experiments on two men (K. B. and R. R.), each of whom ate ice cream at the same temperature (1.4 F). K. B. ate the ice cream in 2.06 minutes, and had a decrease in gastric temperature of 20 F. and a recovery time of 46.8 minutes. R. R. ate the the ice cream in 5.52 minutes, and had a decrease in gastric temperature of 8.6 F. and a recovery time of 37.3 minutes.

The apparent influence of the temperature of the ice cream is shown by the experiments on two women (B. B. and A. J.), each of whom required approximately the same time (1.96 and 1.98 minutes, respectively) to ingest the ice cream. B. B. ate ice cream having a temperature of 17.6 F., and had a decrease in gastric temperature of

2.6 F. and a recovery time of 24.2 minutes. A. J. ate ice cream having a temperature of 13.3 F., and had a decrease in gastric temperature of 14.9 F. and a recovery time of 30.7 minutes.

The apparent influence of the subject is shown by the experiments on two other women (A. S. and A. B.), each of whom ate ice cream having a temperature of 6.8 F. in approximately the same time (3.02 and 3 minutes, respectively). A. S. had a drop in gastric temperature of 8.8 F. and a recovery time of 42.5 minutes; A. B., a drop in gastric temperature of 12.5 F. and a recovery time of 26.3 minutes.

Apparently the decrease in gastric temperature was not governed by the amount of ice cream ingested. This is shown by the following experiments on 2 subjects, a man and a woman, each of whom was accustomed to eating large amounts of ice cream. Each subject performed the routine experiment on ice cream, and, in addition, on a later date, ingested several standard portions at one sitting. The man ate 90 Gm. (temperature, 6.8 F.) in 1.81 minutes; the decrease in gastric temperature was 43.8 F. and the recovery time, 40.3 minutes. He ate 540 Gm. (temperature 14 F.) in 9 minutes; the decrease in gastric temperature was 24.1. He insisted on changing his position after eating the ice cream, and this caused the loss of the test meal by emesis; therefore the recovery time could not be obtained. The woman ate 90 Gm. (temperature, 6.8 F.) in 2.7 minutes; the decrease in gastric temperature was 7.2 F., and the recovery time, 48 minutes. She ate 450 Gm. (temperature, 12.2 F.) in 8.05 minutes; the decrease in gastric temperature was 13 F., and the recovery time, 97 minutes.

Hot Coffee.—In these experiments, the volume of a portion of coffee varied between 140 and 350 cc. Such variations actually occur in practice, between a small cup, on the one hand, and a mug, on the other. The maximum temperature at which coffee may be ingested without discomfort varies markedly with the subject; in a series of eleven experiments (seven on men and four on women), it was found to lie between 113 and 149 F. On ingestion of hot coffee, an immediate, marked increase in gastric temperature occurred, followed by a decrease at first rapid, then progressively slower; finally, the graph again became a straight line which recorded exactly the same temperature for at least 10 minutes. The final temperature of the stomach tended to be slightly higher than its initial temperature, the average difference between the two temperatures being 0.1 F. The time required to drink the coffee was from 0.18 to 4.12 minutes. The increase in gastric temperature ranged between 4.2 and 17 F., and the recovery time between 19.9 and 45 minutes, exceeding 30 minutes in seven experiments.

Possible Effect of Cold Drinks on the Temperature of the Upper Part of the Intestine.—In the earlier experiments on the temperature of the upper part of the intestine, the resistance thermometer was passed in the usual manner, and a roentgenograph was taken. A meal of barium sulphate, chilled as usual, was administered, and another roentgenograph was taken, the subject being in the prone position at each exposure. Then the thermometer was removed. If the thermometer had not been in the intestine, the experiment was discarded.

In a series of nineteen successful experiments of this type (nine on men and ten on women) a decrease in the temperature of the upper part of the intestine followed the ingestion of the meal of chilled barium sulphate. This decrease was as little as 2 F., and as great as 16 F. This distinct decrease was immediately followed by an equally distinct increase. The decrease doubtless was due to leakage of a portion of the meal through the pylorus about the thermometer tube. Such leakage is apparent on some of the roentgenographs.

INFLUENCE OF PHYSICAL THERAPY ON GASTRO-INTESTINAL TEMPERATURE

Study was made of the influence on visceral temperature of the following forms of physical therapy: ice bag, hot wet pack, hot water bag, electric pad, infra-red lamp and diathermy. In one series, each form was applied over the true epigastric region. In another series, each form except the hot wet pack was applied over the region of the upper part of the intestine. There were twelve gastric hot wet pack experiments, divided approximately equally between the two sexes. The other experiments included thirty-four on the stomach and thirty-one on the upper part of the intestine; they were divided approximately equally between the two sexes, and between the five forms of physical therapy.

Each subject was undressed and put to bed. The ice bag and the hot water bag were applied by nurses in the usual clinical fashion. The electric pad was of the "three heat" variety; it was placed in its linen cover and applied directly to the surface of the skin, and used at either the high or the medium heat. The infra-red lamp and the diathermy were applied by the licensed physical therapeutists of the hospital. For diathermy, the anterior plate ranged from 3 by 3 inches (7.6 by 7.6 cm.) to 4 by 9 inches (10.16 by 22.9 cm.), the posterior plate from 4 by 5 inches (10.16 by 12.7 cm.) to 7 by 10 inches (17.78 by 25.4 cm.); the milliamperage almost always varied during a single experiment, and was as low as 500 and as high as 2,900. For the hot wet pack, a hot wet bath towel was placed directly over the skin, and covered with a sheet of rubber dam, over which the electric pad was placed, usually at high heat.

Each agent was applied to the anterior surface of the body. The exact surface area to which the agent was applied was determined in each case by comparison at the bedside with the roentgenographs. With each form of physical therapy, application was made of the maximum heat (or cold with the ice bag) which the individual subject found comfortable.

In each experiment, a mercury thermometer was used to measure the skin temperature. The bulb of the thermometer was placed in the middle of the true epigastric region in the experiments on the stomach, and immediately over the position of the resistance thermometer in experiments on the upper part of the intestine. The bulb was fastened to the skin firmly by means of adhesive tape; the stem of the thermometer was parallel to the long axis of the body. The bulb and a portion of the stem were covered by any physical therapeutic agent applied to the body surface. The skin temperature was read and recorded prior to the application of the agent and at frequent intervals during the course of the experiment.

The maximum skin temperatures observed during the application of the various forms of heat therapy were: hot wet pack, 109.4 F.; hot water bag, 129.2; electric pad, 134.6; infra-red lamp, 136.4, and diathermy, 105.8. The minimum skin temperature observed during the application of the ice bag was 44.6 F.

The period of application of the physical therapeutic agent extended from 35 to 140 minutes, and exceeded an hour in all but eleven of the seventy-seven experiments.

No distinct and uniform tendency to produce either an increase or a decrease in visceral temperature was observed on the application of the hot wet pack, the hot water bag, the electric pad or the infra-red lamp.

On application of the ice bag, a distinct tendency existed for a decrease in the temperature of the stomach and of the upper part of the intestine. In one experiment, an ice bag was applied for 10 minutes to the anterior body surface over the sigmoid with the subject in the Sims position; it produced no appreciable change in the sigmoidal temperature.

On application of diathermy, the visceral temperature uniformly increased, the average increase being 1 F. One man was used in two different experiments on the influence of diathermy on duodenal temperature. In each experiment, the period of application was approximately an hour. In one experiment, the milliamperage was gradually increased from 1,000 to 2,900, and the duodenal temperature increased 1 F. In the other experiment, the milliamperage was kept constant at 1,600, and the duodenal temperature increased 1.2 F.

As stated before, the subjects were in the supine position, and the physical therapeutic agent applied to the anterior surface of the body, since this is the usual clinical procedure. However, one experiment was made with a subject in the prone position in order to bring the abdominal viscera closer to the agent. When in the supine position the subject had shown a slight increase (0.5 F.) in gastric temperature with a hot wet pack. In the prone position, with an electric pad at high heat, her gastric temperature increased by 0.2 F.

None of the observed changes in visceral temperature exceeded the maximum variation in gastric temperature during similar periods of time as reported previously.

FRACTIONAL GASTRIC ANALYSIS AFTER INGESTION OF ICE WATER

A series of experiments was made on men who had been used in the study of the effect of ice water on gastric temperature. Two fractional gastric analyses were made in each experiment, the test meal being given after emptying the stomach; a period of one or more days intervened between the two analyses. Prior to the one analysis, the usual Ewald test meal was given; the tap water had a temperature between 63.5 and 85 F. Prior to the other analysis, an Ewald test meal with ice water (temperature, from 33.8 to 37.4 F.) was used. In each analysis fractions were withdrawn at intervals of 15 minutes; titrations were made by the Töpfer method for free hydrochloric acid, combined hydrochloric acid and total acidity; a sample of 1 cc. and centinormal sodium hydroxide solution were used in each titration.

When ice water was used, the gastric emptying time of the subject was increased by 15 minutes in four experiments, and by 30 minutes in four experiments. No change in emptying time was found in one experiment. Ingestion of ice water exerted no uniform effect on either the maximum concentration of any of the forms of acidity or the time of occurrence of these maximum values. Therefore, the actual numerical results of the acidity determinations have been omitted.

SUMMARY AND CONCLUSIONS

A recording resistance thermometer has been used to measure temperatures in the gastro-intestinal tract. In a group of 257 healthy, active subjects, the gastric temperature was between 97.5 and 102.2 F., (average 99.3 F.) and tended to be approximately 1 degree higher than the oral temperature. In a group of 53 subjects, the temperature of the upper part of the intestine lay between 98 and 100.1 F. (average 99 F.), and was within 1 degree of the gastric temperature. In a group of 6 subjects, the sigmoidal temperature lay between 100.8 and 101.5 F. (average 101.2 F.), and was higher than the oral temperature by 2 degrees or more.

Ingestion of either ice water (250 cc.) or ice cream (90 Gm.) produced a marked decrease in gastric temperature, followed by a rise, at first quite rapid, then progressively slower. The average recovery time was in excess of one-half hour. Use of ice water in a test meal delayed the gastric emptying time by from 15 to 30 minutes.

Evidence was obtained that leakage of a cold beverage through the pylorus lowers the temperature of the upper part of the intestine by

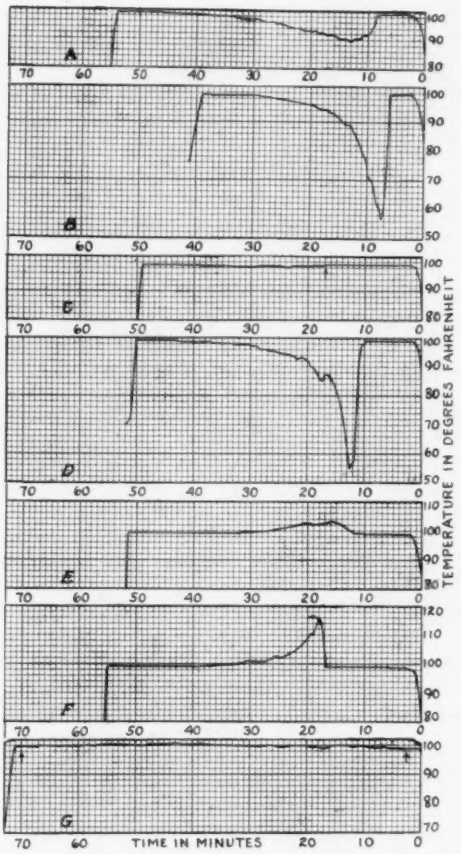

Fig. 2.—Changes in visceral temperature. Each graph is read from right to left. A rise in temperature at the right margin is due to swallowing. Graphs *A* to *F* record gastric temperature; graph *G*, duodenal temperature. Graph *A* records the mininum observed effect of ice water; graph *B*, the maximum observed effect of ice water; graph *C*, the minimum observed effect of ice cream (the arrow denotes beginning of ingestion); graph *D*, the maximum observed effect of ice cream; graph *E*, the minimum observed effect of hot coffee; graph *F*, the maximum observed effect of hot coffee; graph *G*, the maximum observed effect of any form of physical therapy. Diathermy was applied during the period between the arrows.

several degrees. This observation may throw light on the etiology of gastro-enteric disturbances in patients who have a rapid gastric emptying time and partake copiously of cold beverages.

Ingestion of hot coffee produced a marked increase (maximum increase, 17 F.) in gastric temperature, followed by a decrease, at first rapid, then progressively slower.

Physical therapeutic agents (electric pad, hot water bag, infra-red lamp, diathermy, hot wet pack and ice bag) were applied over either the stomach or the upper part of the intestine, usually for an hour or longer. None of the observed changes in visceral temperature exceeded the maximum variation in gastric temperature during similar periods of time in a control series.

The application of heat to the abdomen produces a feeling of comfort when localized or general pain exists. However, in view of the results obtained in this research, the production of any reparative benefit by local application of heat or cold is conjectural. It is doubtful that the benefit obtained is sufficient to warrant subjecting the patient to the various local applications of heat, especially in summer. Consultation with several physiologists has not produced any explanation of the process resulting in the feeling of comfort. The results also render debatable the use of ice locally for the control of gastric or intestinal hemorrhage, and the local application of heat to promote the healing of gastric or duodenal ulcer.

CHANGES IN GASTRIC ACIDITY IN PEPTIC ULCER, CHOLECYSTITIS AND OTHER DISEASES

ANALYZED WITH THE HELP OF A NEW AND ACCURATE TECHNIC

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For fifty years the study of gastric acidity in disease has been hampered, first, by the absence of detailed standards of normal for persons of varying age and sex and, second, by a cumbersome method of classifying acidity, a method that tends to obscure any but large differences between two sets of data.

We recently published standards of normal based on the records of 3,746 persons. The reader is referred to that paper [1] for many details in regard to technic and other matters.

Our standards for free and total acidity and for the incidence of achlorhydria in adults will be found in table 1. So far as children and young persons aged less than 20 years are concerned (table 2), we can provide standards only for free acidity because our data were meager and unsatisfactory in regard to total acidity and the incidence of achlorhydria.

In our previous article we did not analyze the data regarding gastric content removed. We have now done this, and include the more important statistical constants in table 1.

PLAN OF STUDY

For the purpose of this study we calculated for each diseased person in whom free acid was demonstrated the difference between his or her observed free acidity and the normal for a person of corresponding sex and age, and then took the mean of these differences as an index of the

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† Working on a grant from the Josiah Macy, Jr., Foundation.

1. Vanzant, F. R.; Alvarez, W. C.; Eusterman, G. B.; Dunn, H. L., and Berkson, J.: The Normal Range of Gastric Acidity from Youth to Old Age: An Analysis of 3,746 Records, Arch. Int. Med. **49**:345 (March) 1932.

deviation from normal of all the patients with the particular disease under consideration. A similar procedure was carried out in determining the difference from normal of the total acidity and the volume of gastric contents removed.

It should be noted that here again, just as during the study of normal persons, we have not averaged in the readings of persons lacking free acid. Instead we have compared the percentage incidence of achlorhydria in each five-year group with the normal incidence for that group, and have then averaged these differences so as to obtain the mean deviation from normal of the whole group. For convenience in comparison we have expressed this difference also as a percentage of the

TABLE 1.—*Normal Standards for Free and Total Acidity, Volume and Achlorhydria of Adults* *

	Males								Females							
	Free Acid, Units		Total Acid, Units		Volume, Cc.		Achlorhydria, per Cent		Free Acid, Units		Total Acid, Units		Volume, Cc.		Achlorhydria, per Cent	
Age	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	True	Apparent	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	True	Apparent
24-20.....	46.7	16.5	63.5	16.5	118.0	49.5	....	....	32.0	14.5	49.7	14.5	100.5	39.0	2.0	3.0
25-29.....	47.0	17.0	63.0	16.2	116.5	50.5	....	2.0	33.0	14.0	50.0	14.2	100.0	39.0	4.5	6.5
30-34.....	47.0	16.7	62.5	16.2	113.5	50.0	3.0	5.2	33.0	13.7	50.5	14.7	99.0	39.0	7.3	10.0
35-39.....	47.0	16.5	61.7	16.4	109.5	48.5	6.3	8.5	33.0	14.0	50.5	15.1	97.7	39.0	10.0	13.5
40-44.....	46.5	16.5	60.7	17.2	105.0	46.0	9.5	11.7	33.0	13.8	50.5	15.2	96.0	39.0	12.7	17.0
45-49.....	45.5	16.7	59.5	18.4	101.0	43.0	12.7	15.0	33.0	13.5	50.5	14.2	94.0	38.5	14.5	20.5
50-54.....	43.7	17.6	58.3	19.1	97.5	41.0	16.0	18.5	33.0	14.0	50.5	14.7	92.0	37.5	18.2	24.0
55-59.....	41.5	18.7	57.0	19.2	95.0	42.0	19.3	21.5	33.5	15.0	50.5	15.3	89.5	37.0	21.0	27.5
60-64.....	39.3	19.4	55.5	18.8	93.5	45.0	22.0	25.0	33.5	16.0	50.5	16.0	87.0	36.0	23.5	31.0
65-69.....	37.3	18.5	53.7	17.5	92.0	47.0	22.5	26.0	33.5	16.0	50.5	16.7	84.0	35.0	26.3	31.5
70-79.....	33.5	17.0	50.5	16.7	91.0	50.5	17.0	21.0	33.5	15.2	50.5	17.2	79.0	33.0	24.0	28.7

* The mean values given in this table are different from those given in our previous publication (Vanzant, F. R.; Alvarez, W. C.; Eusterman, G. B.; Dunn, H. L., and Berkson, J.: Arch. Int. Med. **49**: 345 [March] 1932) by a constant correction.

incidence of achlorhydria that would be expected in a group of normal persons with a similar age distribution. An example of the arithmetic used in the several processes mentioned is given in an appendix at the end of the paper.

The test meal employed at the Mayo Clinic is of the Ewald type, and consists of 8 arrowroot cookies and 400 cc. of water. After one hour a sample of gastric contents is removed with the small Sawyer tube; it is tested for free acid and if this is present the stomach is emptied and the tube is withdrawn. If, however, there is no free acid, the tube is left in and three more samples are removed at intervals of fifteen minutes. The results of titration are expressed in the usual terms of cubic centimeters of tenth-normal sodium hydroxide required to neutralize 100 cc. of gastric juice.

In the work on normal standards, and also in this paper, we have in every case used the figures for free acid obtained at the end of the first hour. The only use made of subsequent readings with the fractional test has been to help in distinguishing between what we call true and apparent achlorhydria. By true achlorhydria we mean a condition in which none of the several fractions removed in the course of the second hour showed free acid; by apparent achlorhydria we mean a condition in which the first sample did not show free acid but later samples did.

We do not wish at this point to enter into any controversy as to the number of these cases of achlorhydria in which on repeated tests, or with the stimulus of histamine, free acid might have been shown. We

TABLE 2.—*Normal Standards for Free Acid in Children and Youths* *

Age, Years	Males		Females	
	Mean	Standard Deviation	Mean	Standard Deviation
1	5.5	7.3	4.0	8.4
2	12.0	8.0	9.0	8.8
3	17.0	8.5	13.0	9.2
4	20.5	9.0	16.0	9.6
5	23.0	9.6	18.5	10.0
6	24.5	10.2	20.5	10.5
7	26.0	10.8	21.8	11.0
8	26.5	11.3	23.0	11.4
9	27.0	11.7	23.5	11.8
10	27.5	12.0	24.0	12.2
11	27.5	12.5	24.3	12.5
12	28.0	13.0	24.5	12.9
13	30.0	13.5	24.8	13.4
14	33.0	14.0	25.0	13.7
15	37.0	14.5	26.0	14.0
16	41.5	14.9	26.5	14.2
17	44.5	15.2	28.0	14.4
18	45.5	15.5	29.0	14.6
19	45.8	15.7	30.0	14.6
20	46.0	16.0	31.3	14.6

* Expressed in clinical units.

are simply reporting the number of cases in which free acid was not demonstrated with the type of test meal which we used.

Because of the uncertainty in regard to the amount of dilution which occurs when the pylorus is blocked, we have omitted from consideration cases in which there was gastric retention, as evidenced by the presence of food residue or of a volume of gastric contents larger than 250 cc.

It is obvious that two distributions may differ not only as regards the value of the mean but also as regards the spread or range of the data; hence it is necessary to compare not only the means but also the standard deviations which give a measure of the spread. Actually in these studies the standard deviations of the data from the several groups of diseased persons were not found to differ significantly from normal, except in a few instances in which they were slightly decreased. Because the variations from normal were so small, the actual figures will not be pub-

lished. The fact that they did not vary from normal indicates simply that when a disease is associated with a variation in gastric acidity, each individual in the group is affected in the same way and to about the same degree.

Although we studied both free and total acidity, the figures for total acidity followed so closely those found in the case of free acidity that it did not seem worth while to publish them.

CHANGES IN ACIDITY ASSOCIATED WITH DUODENAL ULCER

We have studied records of gastric analysis in the cases of 1,495 men and 398 women with duodenal ulcer. The diagnosis was verified at

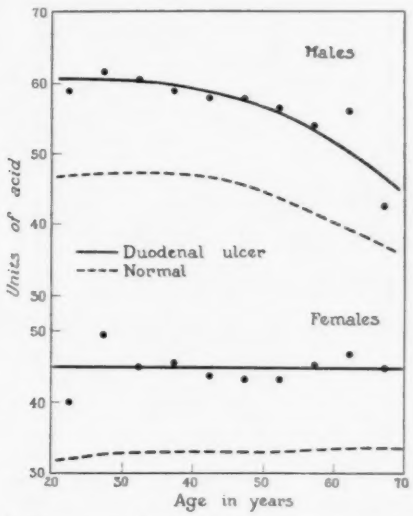

Fig. 1.—Dots indicate mean free acidity for duodenal ulcer in males and in females for each five year age group. Solid lines represent the regression of these points with age. The dotted lines indicate the level of mean acidity in normal persons.

operation on 1,357 of the men and 343 of the women. In the remaining few cases there was a typical clinical history and a definite deformity of the duodenal cap.

As every one knows, duodenal ulcer is commonly associated with an increase in gastric acidity. In our series the mean increase among men was 12.3 units and among women, 11.5 units. Figure 1 brings out the interesting fact that when the figures expressing mean acidity for men and women of different ages were plotted, the curve representing gastric secretion in cases of ulcer was found to be parallel to that representing secretion in normal persons, but it had been shifted upward a distance

corresponding to about 12 units. Apparently, then, these curves represent some biologic variation with age which is so deeply rooted that it is not easily eradicated in disease.

In 13 of the cases of ulcer there was no free acid in the sample of gastric contents removed at the end of an hour, but in 10 of these, later specimens did reveal some free acid. As one of us (Dr. Eusterman [2]) and Palmer [3] have shown, the complete absence of free acid is extremely rare in the presence of duodenal ulcer.

Acidity in the Presence of Severe Symptoms.—In order to see if there was any difference in acidity in the case of patients with mild and severe symptoms of ulcer, we divided the data into two groups: one derived from the study of patients who could easily be treated medically, and the other from patients who had to be operated on. In the men who had been treated medically, the mean free acidity averaged only 7.1 units higher than normal as contrasted with an increase of 12.8

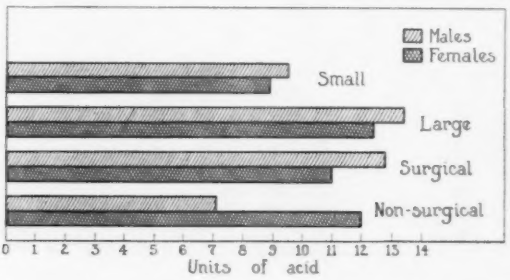

Fig. 2.—The lower two bars represent the increases of free acid above normal in the case of duodenal ulcers which were treated by surgical and nonsurgical measures. The upper bars represent the increased acidity present in the case of ulcers larger than 5 mm., contrasted with that present in the case of smaller ulcers.

units in the men who required operation (fig. 2). There was almost no difference between the mean acidities of the two groups of women.

Of the patients who were treated surgically, 431 had a perforating type of ulcer, while 946 had shallow lesions. No significant difference could be demonstrated between the mean gastric acidities in these two groups, but the patients with small single lesions had from 2 to 3 units less acidity than those with large or multiple lesions.

The volume of gastric contents removed from patients with duodenal ulcer was increased over the normal by an average of 10 cc. This

2. Eusterman, G. B.: Achlorhydria: Practical Consideration of Its Clinical Significance, Northwest Med. **30**:249 (June) 1931.

3. Palmer, W. L.: The Mechanism of Pain in Gastric and Duodenal Ulcer: I. Achlorhydria, Arch. Int. Med. **38**:603 (Nov.) 1926.

increase was slightly less marked among patients with single small ulcers, and in the case of the men with ulcers which were treated medically the mean volume was somewhat less than normal.

The smallness of the increase in volume (10 cc.) of the gastric juice removed is remarkable when one remembers that it has always been taught that duodenal ulcer produces marked hypersecretion and delay in the final emptying of the stomach. It is to be recalled, however, that all cases in which there was definite retention were omitted from the study.

CHANGES OF ACIDITY IN GASTRIC ULCER

In spite of the difficulties which are inherent in the old cumbersome method of summarizing data obtained by gastric analysis, it has been fairly clear to many physicians in the past that the acidity in cases of

TABLE 3.—*Deviations from the Normal in Gastric Ulcer in Men and Women*

	Age, Years			Free Acid, Volume									
				Mean Difference in Units of Acid		Mean Difference, Cc.		Achlorhydria					
								True Difference, per Cent			Apparent Difference, per Cent		
Disease	Patients	Mean	Standard Deviation	Mean	Probable Error	Mean	Probable Error	Mean	Probable Error	Percentage of Normal	Mean	Probable Error	Percentage of Normal
Gastric ulcers—total group	188	44.8	12.0	—5.7	1.2	+14.6	3.0	— 6.5	2.3	46	— 4.0	2.5	75
Large ulcers	116	50.1	7.9	—6.0	1.0	+12.9	3.0	— 9.8	3.1	26	— 8.8	3.3	43
Small ulcers	54	49.9	5.2	—5.4	1.3	+16.1	4.2	— 7.4	4.5	43	— 3.3	4.9	80
Ulcers in proximal third	58	43.9	18.0	—7.9	1.4	+ 7.1	4.1	— 9.3	4.2	23	— 3.3	4.6	80
Ulcers in middle third	66	48.7	8.2	—4.8	1.5	+20.4	3.4	—10.0	4.0	17	— 7.6	4.3	50
Ulcers in distal third	32	48.6	10.5	—3.1	1.6	+35.5	6.2	—10.5	6.0	23	—10.2	6.4	38

gastric ulcer is usually not so high as in cases of duodenal ulcer. Several writers have stated that the acidity in cases of gastric ulcer is not different from normal, but so far as we know, no one has ever recognized the fact that it is lower than normal. So far as achlorhydria is concerned, the impression that we gained from reviewing the literature is that it is present just as often in patients with ulcer of the stomach as in normal persons.

In order that there might be no error in our figures ascribable to mistakes in diagnosis, we selected for analysis the figures for acidity obtained in the case of 160 men and 28 women, in all of whom a gastric ulcer was demonstrated at operation. We excluded data for all patients with gastric stasis due to mechanical obstruction at the pylorus.

In the case of the patients with gastric ulcer the mean free acidity was reduced by an average of 5.4 units in men and 6.6 units in women. Apparent achlorhydria was frequently noted, especially in the case of men, in whom the incidence was only 22 per cent less than normal.

Both men and women had true achlorhydria only half as often as normal. The volume of gastric juice removed at the end of an hour was increased on the average 13.1 cc. in men and 16.6 cc. in women.

Because we wished to see if the size of the lesion had anything to do with the degree of reduction in acidity, we divided the data into two groups: one from patients with lesions less than 5 mm. in diameter, and the other from patients with larger ulcers. Because of the small numbers of cases, the data from men and women were combined. There

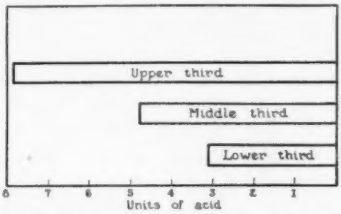

Fig. 3.—The bars show the decreases of mean free acidity below normal in gastric ulcers situated in the upper, middle and lower thirds of the stomach.

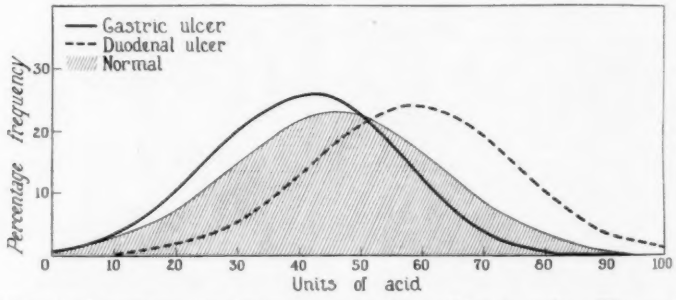

Fig. 4.—Percentage distribution curve for free acidity in males. The gastric ulcer and duodenal ulcer curves give the percentage occurrence of free acids in these groups. The shaded area gives the percentage occurrence for a group of normal persons of the same ages. It is to be noted that both pathologic groups overlap considerably with each other and with the normal, although their means are significantly different.

appeared to be a slightly greater reduction in acidity with the larger ulcers, but the difference was not great enough to be convincing.

We next looked for differences in acidity corresponding to differences in the situation of the ulcer in the stomach, and an interesting gradation was found. Ulcers at or near the pylorus were associated with acid values which were not significantly different from the normal. With ulcers in the middle third of the stomach the acidity was reduced

by 4.8 units, while with ulcers in the upper third it was reduced by 7.9 units (fig. 3 and table 3). A similar observation was made years ago by Smithies.[4]

As was to be expected, although the acidity of the secretion was affected to a greater degree with lesions high in the stomach than with lesions near the pylorus, the reverse was true with respect to the volume of secretion. Ulcers near the pylorus increased the volume by 35.5 cc., those in the middle third increased it by 20.4 cc. and those in the upper third had no effect on it.

It is obvious, then, that gastric acidity in cases of ulcer of the stomach and of ulcer of the duodenum is altered from the normal in opposite directions (fig. 4). Several hypotheses might be advanced to explain this fact, but any theorizing at this time would be of so little value that we shall not attempt it.

MEAN GASTRIC ACIDITY IN THE PRESENCE OF GASTRO-JEJUNAL ULCER

Gastric acidity is usually lowered by gastro-enterostomy, but when in an occasional case a jejunal ulcer forms, it is commonly assumed that the acids of the stomach have remained high.

For the purposes of this study we analyzed data from 174 men and 14 women with an anastomotic ulcer demonstrated surgically. The mean free acid was less than normal among the men by 3.7 units and among the women by 10.8 units. When it is remembered that these patients had all been operated on previously for duodenal ulcer, in which condition the acidity is usually high, it is apparent that a great lowering in mean acidity had occurred since operation. Among the men this loss must have averaged 16.5 units and among the women, 22.2 units.

None of the 14 women had achlorhydria, but some of the men did. Among them the incidence of this peculiarity was not so high as among normal persons, but it was many times higher than that of patients with duodenal ulcer. This does not mean necessarily that the stomachs of these persons were incapable of secreting acid, but perhaps only that during the time when the test was being made the acid formed was being neutralized as fast as it was secreted.

The amount of gastric secretion removed from the stomachs of men at the end of an hour was practically the same as in the case of duodenal ulcer. Among the women the increase was three times this, or about 30 cc., but the group was so small that this observation cannot be stressed.

4. Smithies, Frank: Gastric Ulcer Without Food Retention: A Clinical Analysis of One Hundred and Forty Operatively Demonstrated Cases, Am. J. M. Sc. **145**:340 (March) 1913.

CAN ONE DETECT A SETTING FOR GASTROJEJUNAL ULCER?

In the case of 50 of the patients with gastrojejunal ulcer, all men, we had a record of the gastric acidity present before gastro-enterostomy. The mean free acidity of these patients was 12.5 units above normal, which is almost exactly the figure that was found in patients with duodenal ulcer who were treated surgically. In no instance was there achlorhydria. The volume of gastric secretion was increased by 15.6 cc., which is 4 cc. more than the increase in the group of patients with duodenal ulcer severe enough to require operation.

The only conclusion possible from this study of gastric acidity of patients who submitted to gastro-enterostomy for the relief of duodenal ulcer is that there is no difference in mean gastric acidity in the two groups of cases in which jejunal ulcer develops later, and in those in which it does not. In other words, there is no warrant for the commonly held belief that one can, by measuring gastric acidity, recognize those cases of duodenal ulcer in which gastro-enterostomy is likely to be followed by the development of gastrojejunal ulcer.

The fact that studies of the gastric acidity have failed to help us at this point has not discouraged us from continuing to look for significant peculiarities in other constituents of the gastric juice, such as pepsin.

EFFECT OF CHOLECYSTITIS ON MEAN GASTRIC ACIDITY

The impression gained from the voluminous literature on the subject is that cholelithiasis and acute cholecystitis may cause an increase in gastric acidity, whereas chronic cholecystitis is frequently associated with subacidity or achlorhydria. Some investigators, however, have concluded that there is no significant change in gastric acidity in cases of cholecystitis.

For the purposes of this study we took records from 602 cases in which the diagnosis of cholecystitis, with and without stones, was confirmed at operation. In both groups the mean free acidity was not significantly different from normal in either men or women. Neither was there any difference in the volume of secretion such as would indicate that there is commonly a change in the emptying time of the stomach. There was, however, a slight increase in the incidence of achlorhydria of men.

Cholecystectomy.—Meyer, Ivy and McEnery [5] found in experimental animals that cholecystectomy commonly produced slight hypersecretion, but no definite evidence of this has been found in the case of man. Hartman and Rivers [6] were unable to show any constant alteration, but

5. Meyer, Jacob; Ivy, A. C., and McEnery, E. T.: The Effect of Cholecystectomy on Gastric Secretion, Arch. Int. Med. **34**:129 (July) 1924.

6. Hartman, H. R., and Rivers, A. B.: The Effect of Cholecystectomy on Gastric Acidity, Ann. Int. Med. **1**:558 (Feb.) 1928.

we thought it worth while to reinvestigate the problem with the new and more accurate method of statistical analysis. In this study we used records from the cases of 59 men and 118 women. The interval between cholecystectomy and gastric analysis varied from a few months to several years. In the case of men there was a lowering of mean free acid by about 4 units, but this could not be shown in the case of the women. There were curious changes from normal in the incidence of achlorhydria, but on account of the small size of the groups their significance is doubtful.

Cholecystitis in Association With Duodenal Ulcer.—Cholecystitis and duodenal ulcer are so commonly associated that we wished to know what effect the combination would have on gastric acidity. For purposes of analysis we took records from the cases of 125 men and 89 women. All of the patients had been operated on for duodenal ulcer, and all of them had either submitted to cholecystectomy or were found to be suffering from cholecystitis at the time of operation for ulcer. In these cases free acid was increased by 13.3 units in the men and by 12.6 units in the women. These figures are approximately 1 unit higher than in the case of surgical duodenal ulcer alone. The volume of secretion was normal in the men and greatly increased in the women.

ALLERGY

In a recent article Bray [7] published his observations on a group of 200 asthmatic children in whom he found gastric acidity markedly lower than normal, and the frequency of achlorhydria increased. He suggested that with the lowering of digestive power in the stomach there might be an increase in absorption of incompletely split proteins which, in turn, might sensitize the patient and produce the asthma.

Little is known about the gastric acidity of adults suffering from allergic types of disease, but the general impression is that there is a lessening in the amount of acid. We observed 34 men and 43 women who suffered from various conditions such as urticaria, angioneurotic edema and asthma. The mean acidity of the men was lower than normal by 3.6 units; that of the women was higher than normal by 3.4 units. On account of the smallness of the groups these differences cannot be considered significant. The incidence of achlorhydria was slightly less than expected, but again the difference was not large enough to be significant.

There seems to be little doubt about the lowering of gastric acidity of children with asthma. On comparing Bray's published data with our standards of normal the mean free acid was found to be lowered by 9.6 units.

7. Bray, G. W.: Hypochlorhydria of Asthma in Childhood, Quart. J. Med **24**:181 (Jan.) 1931.

TABLE 4.—*Deviations from Normal in Various Diseases*

Disease	Patients	Age, Years		Free Acid		Volume		Achlorhydria					
								True			Apparent		
				Mean Difference in Units of Acid		Mean Difference, Cc.		Difference in per Cent			Difference in per Cent		
		Mean	Standard Deviation	Mean	Probable Error	Mean	Probable Error	Mean	Probable Error	Per Cent of Normal	Mean	Probable Error	Per Cent of Normal
Men													
Duodenal ulcer, total group	1,405	42.5	10.8	+12.3	0.2*	+10.8	1.5*	— 9.3	0.7*	3	—11.4	0.8*	10
Medically treated	138	45.4	11.7	+ 7.1	1.0*	— 3.0	2.2	—10.6	2.6*	0	—12.7	2.8*	13
Surgically treated	1,357	42.3	10.7	+12.8	0.3*	+11.6	1.6*	— 9.1	0.8*	3	—11.2	0.9*	10
Penetrating type of ulcer	431	43.3	11.4	+13.3	0.6*	+12.7	1.7*	.....	...	...	.....	...	...
Shallow ulcers	926	42.6	10.5	+12.6	0.4*	+11.1	1.5*	.....	...	...	.....	...	...
Multiple ulcers	167	41.2	10.1	+13.4	0.9*	+13.2	2.7*	.....	...	...	.....	...	...
Single large ulcers	188	42.1	9.7	+13.4	2.6*	+10.5	2.6*	.....	...	...	.....	...	...
Single small ulcers	87	40.0	9.0	+10.5	1.2*	+ 4.0	3.2	.....	...	...	.....	...	...
Developed jejunal ulcer later	50	39.2	13.2	+12.5	1.3*	+15.4	3.0*	.....	...	...	.....	...	...
Gastrojejunal ulcer	174	41.6	10.1	— 3.7	1.0*	+10.1	3.3*	— 2.1	2.2	71	— 1.5	2.4	86
Gastric ulcer, total group	160	44.3	12.3	— 5.4	0.9*	+16.6	2.6*	— 6.0	2.4	46	— 2.9	2.6	78
Cholecystitis	95	44.8	11.7	— 2.8	1.2	+ 0.1	3.0	+ 2.9	3.1	127	+ 3.7	3.4	127
Cholelithiasis	86	48.8	10.2	+ 0.7	2.2	+ 1.6	4.8	+ 1.7	3.6	113	+ 1.6	3.9	110
Postcholecystectomy	59	51.0	11.7	— 4.2	1.5*	+ 6.1	3.4	— 4.1	6.4	71	+ 3.6	6.9	121
Cholecystitis and duodenal ulcer	125	44.3	10.6	+13.3	1.1*	+ 0.3	2.8	— 9.8	2.5*	1	—12.0	2.8*	1
Allergic disease	34	42.5	13.4	— 3.6	1.9	.....	...	— 0.6	4.8	93	— 2.6	5.3	78
Migraine	97	40.3	10.1	— 0.7	1.2	— 4.6	2.7	— 4.5	2.8	48	— 4.4	3.1	55
Psychoneurosis	185	39.5	11.7	+ 1.3	0.9	—10.6	2.2*	+ 4.1	1.9	158	+ 4.0	2.2	140
Chronic nervous exhaustion	339	40.4	10.8	+ 0.6	0.6	+ 7.7	2.0*	+ 1.9	1.5	122	0.0	1.7	100
Women													
Duodenal ulcer, total group	443	44.3	10.4	+11.1	0.6*	+14.3	1.6*	—12.7	1.6*	7	—16.6	1.8*	12
Medically treated	100	44.6	8.7	+11.0	1.2*	+10.5	2.8*	—13.0	3.3*	7	—16.5	3.6*	11
Surgically treated	343	44.2	10.6	+11.4	0.6*	+15.3	1.8*	—12.4	1.8*	7	—16.6	2.0*	12
Penetrating type of ulcer	74	46.6	11.3	+10.9	1.1*	+22.7	3.6*	.....	...	...	.....	...	...
Shallow ulcers	260	43.4	10.6	+11.6	0.6*	+13.2	2.0*	.....	...	...	.....	...	...
Multiple ulcers	39	41.4	9.7	+11.5	1.2*	+ 1.7	2.5	.....	...	...	.....	...	...
Single large ulcers	52	40.3	14.1	+12.4	1.4*	+10.0	2.1*	.....	...	...	.....	...	...
Single small ulcers	39	45.7	16.0	+ 8.9	1.3*	+ 9.7	4.3	.....	...	...	.....	...	...
Gastrojejunal ulcer	14	41.5	10.2	—10.8	2.3*	+25.0	7.3*	.....	...	0	.....	...	0
Gastric ulcer, total group	28	47.7	10.5	— 6.6	1.8*	— 1.2	4.5	— 8.4	6.8	46	— 9.9	7.5	46
Cholecystitis	224	43.3	10.0	— 0.8	0.6	+ 3.1	2.1	— 0.5	2.2	96	— 1.4	2.5	92
Cholelithiasis	197	46.7	11.3	— 0.3	0.7	— 1.3	1.1	— 2.3	2.5	85	— 3.5	2.8	82
Postcholecystectomy	118	45.9	11.2	— 0.2	0.9	.....	...	— 0.2	3.2	99	— 3.7	3.5	78
Cholecystitis and duodenal ulcer	89	46.8	10.7	+12.6	1.1*	+33.9	3.5*	—15.1	3.8*	0	—20.3	4.1*	0
Allergic disease	43	39.1	13.2	+ 3.4	1.5	.....	...	— 1.6	4.5	85	— 0.7	5.2	95
Migraine	140	40.8	10.0	+ 2.4	0.8*	+ 0.5	2.6	0.0	2.8	100	— 1.7	3.1	99
Psychoneurosis	156	42.2	12.3	— 1.0	0.8	— 4.1	2.3	+ 0.8	2.6	106	+ 0.5	2.9	100
Chronic nervous exhaustion	535	42.3	11.8	— 0.8	0.4	— 2.2	1.3	— 2.5	1.4	80	— 3.6	1.6	78

* Probable error is less than one third the corresponding mean value, indicating that this value is statistically significant.

MIGRAINE

Migraine is of great interest to the gastro-enterologist because it so often produces nausea and vomiting and gastric stasis. We observed 97 men and 140 women in all of whom a gastric analysis was made during the interval between headaches. The mean free acid of the men was 0.7 units below normal, and the incidence of achlorhydria was half the normal one. The mean free acid of the women was increased by 2.4 units and the incidence of achlorhydria was normal. The volume of gastric secretion was apparently normal.

Our impression is that none of the slight differences found is clinically significant.

PSYCHONEUROSIS AND CHRONIC NERVOUS EXHAUSTION

One hundred years ago Beaumont [8] noticed that anger caused a drying of the gastric mucosa in the case of Alexis St. Martin. Since then many observations have been made, all indicating that anxiety and painful emotion can produce marked inhibition of gastric secretion and motility. There are reports in the literature of lower acidity in patients suffering from melancholia. Most of these patients were confined to asylums and therefore must have been much more seriously affected than were our patients who came of their own accord to the clinic. There were 186 men and 156 women, all of whom were suffering with a psychoneurosis, usually of the anxiety type. In addition to the patients with psychoneurosis there were 337 men and 535 women suffering with chronic nervous exhaustion, and showing symptoms of emotional instability. In both groups the mean free acid of the men was slightly but not significantly higher than normal. Among the women there was practically no difference from the normal.

Among the men with psychoneurosis the incidence of achlorhydria was increased by 58 per cent, and among men with nervous exhaustion it was increased by 22 per cent. On the other hand, among women with psychoneurosis the incidence of achlorhydria was normal, and among those with chronic nervous exhaustion it was 20 per cent below normal. These observations are hard to understand and in view of the large probable error their significance is questionable. In none of the groups was there any significant difference from normal in the volume of gastric contents.

COMMENT

We believe that the new method of analyzing gastric acidity in disease has several advantages over the old. First, we use more detailed standards of normal; second, we express a deviation from normal in

8. Beaumont, William: The Physiology of Digestion With Experiments on the Gastric Juice, ed. 2, Burlington, Vt., Chauncy Goodrich, 1847.

simpler terms; third, we can estimate the degree of reliability of any deviation found, and fourth, we can study the degree of overlapping of the distribution curve representing data from diseased persons with the normal curve.

The first three advantages have been stressed in the introduction to the paper. The amount of overlapping of the distribution curves for gastric and duodenal ulcer is shown in figure 4. There it will be seen that even when, as in the case of duodenal ulcer or gastric ulcer, there is a definite shift in the value of the mean, there is still only a small group of cases in which the results of a gastric analysis can have any great diagnostic value. Actually the range of normal is so great that no reading can be pathognomonic of any disease. All one can say is that the probabilities are small or large that a gastric or duodenal ulcer is present.

It should be noted that we have not said that duodenal or gastric ulcer caused a change in acidity; instead we have been careful to say merely that the disease was associated with an increase or decrease in acid values. So far as we can see, our data do not throw any light on the old problem of whether a duodenal ulcer causes hyperacidity, or whether the presence of hyperacidity leads to the formation of an ulcer.

SUMMARY

There was an increase of approximately 12 units of free acidity in the case of duodenal ulcer, an increase which varied with the size of the ulcer, with the number found at operation and with the severity of the symptoms produced. Less than 1 per cent of the patients with duodenal ulcer failed to show free acid after an Ewald test meal.

In 50 cases studied, the gastric acidity of patients with duodenal ulcer who, after gastro-enterostomy, returned with jejunal ulcer was not higher than that of patients similarly operated on who, after two or more years, are still free from symptoms of jejunal ulcer.

In 174 men with gastro-jejunal ulcer, the mean free acidity was lower than normal by about 4 units. The incidence of true achlorhydria was 71 per cent of normal.

In the case of gastric ulcer the mean free acidity was lower than normal by about 6 units. This lowering was more marked in the cases of ulcers situated in the proximal two thirds of the stomach. The incidence of achlorhydria was half of that observed in normal persons.

Practically no change from normal was found in the mean free acidity of patients with cholecystitis and cholelithiasis. No change from normal could be found in the gastric acidity of patients who had submitted to cholecystectomy. In the case of patients who suffered with a combination of disease of the gallbladder and ulcer of the duodenum, the acidity was slightly higher than in the case of patients with uncomplicated duodenal ulcer.

There was no significant deviation from normal in the mean gastric acidity of patients suffering with allergic manifestations, migraine, psychoneurosis and chronic nervous exhaustion. Among the men with a psychoneurosis the incidence of achlorhydria was increased about 50 per cent and among those with migraine it was decreased about 50 per cent. In both groups the incidence of achlorhydria among women was normal.

In the absence of marked organic obstruction at the pylorus it was noted that with duodenal ulcer and gastrojejunal ulcer there was a slight increase in the amount of gastric juice removed; there was also a slight increase in the presence of gastric ulcers situated in the distal two thirds of the stomach.

APPENDIX

Methods of Comparing the Results of Gastric Analysis in a Group of Diseased Persons With Those in a Normal Group of the Same Age and Sex Composition.—So far as concerns gastric acidity and volume recovered, a simple procedure is to express the reading of each patient as a deviation, in actual units, from the mean value of the normal standard for the patient's sex and age. These differences, plus and minus, are then added algebraically and an average obtained. If the group being studied is normal as to gastric acidity or volume, as the case may be, this average will be zero or will not differ significantly in a statistical sense from zero. To know whether a given difference is significant, we must know its probable error; if it is less than three times its probable error it is customary to consider it "not significant." For the particular mean difference with which we deal here, obtained from a standard that varies with every age, the formula for the probable error is not explicitly presented in any statistical reference. However, it may be calculated straightforwardly from elementary statistical theorems. Here space forbids us to present the algebraic derivations, but the results of the analysis together with an example of the arithmetical process used are given. In these examples it will be seen that we do not actually set up each individual difference to obtain an average, but that a more summary method is used. It is to be understood that precisely the same results are obtained as would be by the longer process. On a similar principle the percentage of persons with achlorhydria found in a diseased group is compared with a normal group of the same age and sex.

In tables 5 and 6, capital letters are used to represent functions of the standard group, and small letters functions of the diseased group. An n represents the number of persons in a group studied; M and m represent means; Σ and σ, standard deviations; D, a difference, and P. E., the probable error. In table 6, n_a represents the number in the diseased group with achlorhydria, and P and p represent percentages

Following are examples of calculation in a group of psychoneurotic women.

TABLE 5.—*Free Acidity* *

Age, Years	n	M	Σ	m	σ	n × M	n × m	n × Σ	n × σ	σ²	n × σ²
20-24	9	32.0	14.5	28.4	13.5	288.0	255.6	130.5	121.5	182.25	1,640.25
25-29	15	33.0	14.0	35.2	14.6	495.0	528.0	210.0	219.0	213.15	3,179.40
30-34	22	33.0	13.7	33.0	13.3	726.0	726.0	301.4	292.6	176.89	3,891.58
35-39	22	33.0	14.0	26.7	13.3	726.0	587.4	308.0	292.6	176.89	3,891.58
40-44	10	33.0	13.8	35.0	13.0	330.0	350.0	138.0	130.0	169.00	1,690.00
45-49	15	33.0	13.5	35.9	13.8	495.0	538.5	202.5	207.0	190.44	2,856.60
50-54	20	33.0	14.0	29.6	12.8	660.0	592.0	280.0	256.0	163.84	3,276.80
55-59	7	33.5	15.0	35.4	13.5	234.5	247.8	105.0	94.5	182.25	1,275.75
60-64	8	33.5	16.0	30.8	8.4	268.0	246.4	128.0	67.2	70.56	564.48
65-69	2	33.5	16.0	45.0	11.0	67.0	90.0	32.0	22.0	121.00	242.00
	130					4,289.5	4,181.7	1,835.4	1,702.4		22,526.44

* Total volume is treated similarly.

In example 1 (table 5), $M_M = \frac{4,289.5}{130} = 32.996$. The weighted mean acidity of the comparable normal group.

$M_m = \frac{4,181.7}{130} = 32.166$. The weighted mean acidity of the diseased group.

$D_m = 32.166\text{-}32.996 = -0.830$. The weighted mean difference from the normal standard.

$\sigma_{D_m} = \frac{\sqrt{22,526.44}}{130} = 1.1545$. Standard deviation of D_m.

$P.E._{Dm} = 0.6745 \times 1.1545 = 0.7787$. Probable error of D_m. (In this example the probable error is almost as large as the difference and hence this difference is not statistically significant.)

For the purpose of comparing the spread of the data in the diseased and normal groups we must compute the standard deviations.

$M_\Sigma = \frac{1,835.4}{130} = 14.118$. The weighted mean standard deviation of the comparable normal group.

$M_\sigma = \frac{1,702.4}{130} = 13.095$. The weighted mean standard deviation of the diseased group.

$D_\sigma = 13.095\text{-}14.118 = -1.023$. The weighted mean difference between the standard deviations of the two groups.

$\sigma_{D\sigma} = \sqrt{\frac{22,526.44}{2}} = 0.9816$. Standard deviation of $D\sigma$.

$P.E._{D_\sigma} = 0.6745 \times 0.9816 = 0.66$. Probable error of $D\sigma$.

TABLE 6.—*True Achlorhydria*

Age, Years	n	n_a	P	$n \times P$	$P \times (100-P)$	$n \times P(100-P)$
20-24	11	2	2.0	22.0	196.00	2,156.00
25-29	15	0	4.5	67.5	429.75	6,446.25
30-34	25	2	7.3	182.5	676.71	16,917.75
35-39	25	3	10.0	250.0	900.00	22,500.00
40-44	13	3	12.7	165.1	1,108.71	14,413.23
45-49	18	2	15.5	279.0	1,309.75	23,575.50
50-54	24	2	18.2	436.8	1,488.76	35,730.24
55-59	11	3	21.2	231.0	1,659.00	18,249.00
60-64	10	2	23.5	235.0	1,797.75	17,977.50
65-69	4	2	26.3	105.2	1,938.31	7,753.24
	156	21		1,974.1		165,718.71

In example 2 (table 6), $M_P = \frac{1,974.1}{156} = 12.654$. Weighted mean percentage representing the incidence of achlorhydria in the comparable normal group.

$M_p = \frac{21}{156} \times 100 = 13.461$. Weighted mean percentage representing the incidence of achlorhydria in the diseased groups.

$D_p = 13.461\text{-}12.654 = 0.807$. The weighted mean difference in the percentage of achlorhydria from the normal standard.

$\sigma_{Dp} = \frac{\sqrt{165,718.71}}{156} = 2.61$. Standard deviation of D_p.

$PE_{Dp} = 0.6745 \times 2.61 = 1.76$. Probable error of D_p.

NITROGEN AND SULPHUR METABOLISM IN BRIGHT'S DISEASE

IV. RETENTION OF UREA IN THE NEPHROSIS SYNDROME

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It has previously been noted by Peters and others [1] that patients exhibiting the nephrosis syndrome retain a large proportion of the intake of nitrogen without an increase in the nonprotein nitrogen in the blood, and that even when crystalline urea is added to the diet, it is retained. Peters and Van Slyke [2] thought that the retention of nitrogen serves to make up the loss of body protein chiefly in the form of albumin excreted in the urine. If this is true, it accounts in part for the retention of sulphur noted formerly.[3] So far as I have been able to ascertain, no studies have been made on the relation between the excretion of nitrogen and that of sulphur in this condition when crystalline urea has been added to a diet already high in protein. I shall report metabolism studies on a patient, whose case history was included in the first paper of this series (case 4).[3] It is sufficient to state that she presented a picture typical of lipoid nephrosis (nephrosis syndrome). The significant criteria are given in table 1. The period of study was thirty-six consecutive days, from Feb. 23 to March 31, 1928. On April 1, the patient contracted a fulminating infection, and she died four days later. Her condition during the entire period of study was essentially stationary, and so far as could be determined, the outward evidences of edema did not change. It will be noted in the accompanying chart that she gained slightly in weight despite the diuresis; the entire variation, however, was within about 10 per cent of her weight on admission.

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This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases of Harvard University.

1. Peters, J. P.; Bulger, H. A.; Lee, Carter, and Murphy, C. F.: The Relation of Albuminuria to Protein Requirement in Nephritis, Arch. Int. Med. **37**:153 (Feb.) 1926. Rabinowitch, I. M., and Childs, M. C. C.: A Contribution to the Biochemistry and Treatment of Chronic Nephrosis (Epstein), ibid. **32**:758 (Nov.) 1923. Peters, J. P., and Moor, D. D.: J. Clin. Investigation **6**:5, 1928.

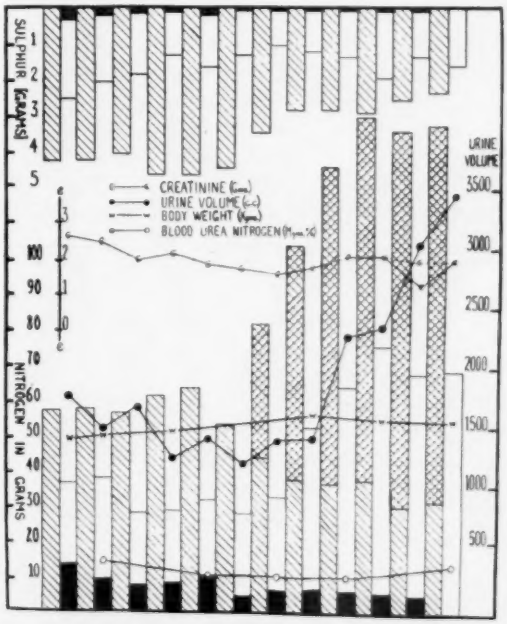
2. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1.

3. Grabfield, G. P.: J. Clin. Investigation **9**:311, 1930.

The chart represents the study in twelve consecutive three day periods. The diet was weighed, and the food refused was weighed. The total intake of fluid was kept constant at 2,500 cc. per day, this figure including the fluid in the food. The food was not analyzed, but standard tables of composition were used. The accompanying chart

TABLE 1.—*Significant Laboratory Findings in Case 4 During the Period of Study*

Date	Phthalein Excretion, Percentage in 2^10'	Total Plasma Protein, Percentage	Serum Albumin, Percentage	Serum Globulin, Percentage	Blood Cholesterol, Mg. per 100 Cc.	Blood Urea Nitrogen, Mg. per 100 Cc.
February 13	70	....	....	....	...	11
February 14	..	4.01	0.97	3.04	246	..
February 25	..	....	....	....	...	15
March 5	..	3.44	0.52	2.92	180	11
March 12	..	....	....	....	471	11
March 19	..	3.92	0.47	3.45	...	11



The nitrogen and sulphur metabolism in case 4 graphically depicted, with other significant findings over a consecutive thirty-six day period. Each double column represents a three day period. The solid black columns represent the output of nitrogen or sulphur in albumin; the diagonally crossed columns, the intake of nitrogen or sulphur in food; the white columns, the output of nitrogen or sulphur; the cross-hatched columns, the intake of nitrogen as urea.

presents the pertinent data; the diagonally crossed and cross-hatched columns represent the intake; the black and the white columns, the output. It should be emphasized that the figures represent nitrogen and sulphur, and not protein or urea. The black portions of the columns for excretion represent the output of nitrogen or of sulphur as albumin. The total albumin was determined by the sulphosalicylic acid method, and the sulphur was calculated as for serum albumin, which contains 1.8 per cent according to Hammarsten's figures. Creatinine was determined as a check on the urinary collections, and it will be seen that this curve runs essentially constant. In the eleventh period, all the figures are corrected as indicated in the creatinine [3a] curve because it was known that some urine was unavoidably lost.

The whole study may be conveniently divided into two periods: eighteen days with urea and eighteen days without urea (table 2). The

TABLE 2.—*Summary of the Figures Shown on the Chart*

	Period I, 18 Days	Period II, 18 Days
Intake of nitrogen, Gm.	354.0	726.0
Output of nitrogen (urine), Gm.	192.0	353.0
Nitrogen retained, Gm.	162.0	373.0
Intake of sulphur, Gm.	26.0	16.7
Output of sulphur, Gm.	10.5	8.3
Sulphur retained, Gm.	15.5	8.4
Nitrogen : sulphur ratios:		
Urine	18.3	42.5
Intake	13.6	43.5
Intake, excluding 506 Gm. of crystalline urea	13.6	13.2
Retained	10.4	44.5

preurea period indicates what has been so often observed in patients with the nephrosis syndrome, namely, a strongly positive nitrogen and sulphur balance amounting to the retention of large quantities of both substances. It is interesting to study a little more closely the relationship between the nitrogen and the sulphur in these two periods. It will be seen that in both periods the ratio of nitrogen to sulphur in the food ingested was 13:1, whereas in the output during the first period the ratio was 18:1. It is evident, therefore, that during the first period more sulphur was retained than nitrogen, and the ratio of nitrogen to sulphur retained was 10:1. In the second period, if one takes into account the total intake of nitrogen minus the output, the ratio is 45:1. If, on the other hand, one considers that all the nitrogen in the urine in the second period came from urea, and that only the protein nitrogen of the diet was retained, the ratio is 26:1. It is evident,

3a. The feces were not analyzed as previous studies have shown that no significant change is made in the results by the fecal nitrogen or sulphur.

therefore, that there is some alteration in the mechanism of the retention of nitrogen and sulphur brought about by the exhibition of large quantities of urea. It is obvious that the sulphur in the urine must come from the breakdown of body or food protein, as the urea contains none. It is obvious, furthermore, from the figures given that some of the crystalline urea is retained in the body. Not only was the total urinary excretion of nitrogen less than the urea nitrogen administered, but if it is assumed that the protein behaved as it did in the preurea period and that the ratio of nitrogen to sulphur in the protein retained was 10:1, the retention of nitrogen from the dietary protein in the second eighteen days would be 124 Gm., which is considerably more than is reasonable from the total figures. It is interesting to note that the excretion of sulphur was slightly greater during the period urea was being administered than during the preurea period, compared with the intake; that is, during the first period almost 60 per cent of the intake of sulphur was retained, whereas in the second period 50 per cent was retained. This difference is possibly not significant; it is merely noted in passing.

The important question centers around the fate of the retained nitrogen. The patient studied was one whose plasma proteins were tremendously depleted, in whom the albumin-globulin ratio was reversed, and who, despite the diet high in protein and the urea, was apparently unable to repair the loss of plasma protein nitrogen. There is some evidence that with a tremendously high intake of urea there is a diminution in the output of nitrogen as albumin, but there is no evidence of regeneration of plasma protein. As to the fate of the retained nitrogen, I can offer no explanation. It obviously does not appear in the blood as nonprotein nitrogen. The quantities that are retained represent nearly 2 Gm. per hundred cubic centimeters of fluid in the entire body, if the body is considered as being 85 per cent composed of fluid. If the retained urea in such patients remains diffusible, it is inconceivable that this would not have been detected in the figures for the urea nitrogen of the blood, which, it will be seen, remained constant and low. The possibility of the storage of all this nitrogen somewhat after the manner of deposit protein is conceivable, though the quantity far exceeds the figures heretofore reported.

During the period urea was being administered, the retention of nitrogen, calculated as "flesh," would amount to $373 \times 6.25 \times 4$, or 9.3 Kg. During this period the weight remained essentially constant, and the diuresis amounted to about 6,000 cc. over and above the preceding level of the urinary output. Therefore, approximately 3 Kg. of tissue has to be accounted for. Unfortunately on the first day of the administration of urea the weight was not recorded, and it may be that the gain shown on the chart, amounting to about 3 Kg., occurred

in that period. In any case, these figures are sufficiently suggestive to make the hypothesis of Van Slyke, that nitrogenous products are retained as "flesh," the likely one. Apparently, judging by these two periods, the body will retain the sulphur-rich moiety of the protein molecule if it is available, but will retain a protein of low sulphur content if only that is available. The significant fact is that this is an indication (though by no means proof) that under conditions such as exist in this patient urea may be converted into protein.

That the whole picture may concern the question of deposit protein and an anomaly of protein metabolism is further emphasized by the analogy between such patients and patients with hypothyroidism, which has been frequently mentioned in the literature. It is striking that in myxedematous persons after the administration of thyroid substance [4] and in normal persons on the administration of iodides,[5] the extra nitrogen that first appears in the urine comes from the sulphur-poor moiety of the protein molecule, indicating that the body in each of these situations holds on most strongly to the sulphur-rich protein. In nephrosis the urinary nitrogen-sulphur ratio is high. These data are reported as an indication of the metabolic problem.

SUMMARY

1. The excretion of nitrogen and sulphur has been studied for a thirty-six day period in a patient exhibiting the nephrosis syndrome.

2. During half of this time, crystalline urea in large quantities was added to the diet. This produced diuresis.

3. Definite evidence is given that crystalline urea is retained but does not appear in the nonprotein nitrogen of the blood.

4. It is suggested that the retained nitrogen is stored as "flesh," possibly to replace the deposit protein which has been called on to maintain the serum proteins lost through the kidneys.

4. Boothby, W. M.; Sandiford, I.; Sandiford, K., and Sloose, J.: Tr. A. Am. Physicians **40**:195, 1925.

5. Grabfield, G. P.: Boston M. & S. J. **197**:1121, 1927.

UREA CLEARANCE TEST IN PREGNANCY

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The studies of Van Slyke and his associates [1] have established on a firm foundation the relation between the concentration of urea in the blood and that in the urine of normal persons under a variety of conditions. As a result of these and of similar investigations, it is generally recognized that the urea clearance test is perhaps the most reliable method available for the quantitative estimation of renal functional efficiency. Certain factors have been shown to affect the rate of removal of urea from the blood of normal persons. As demonstrated by Addis and Drury,[2] MacKay [3] and Van Slyke, Alving and Rose,[4] severe exercise may diminish urea clearance somewhat, presumably by diverting an unduly large proportion of blood to muscular tissues, with a resulting diminution in the renal circulation. Moderate exercise, however, as shown by Van Slyke, Alvin and Rose [4] and by Bruger and Mosenthal,[5] has no significant influence on the blood urea clearance. The relation-

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1. (*a*) Van Slyke, D. D.; McIntosh, J. F.; Möller, E.; Hannon, R. R., and Johnston, C.: Studies of Urea Excretion: VI. Comparison of the Blood Urea Clearance with Other Measures of Renal Function, J. Clin. Investigation **8**:357, 1930; (*b*) Austin, J. H.; Stillman, E., and Van Slyke, D. D.: Factors Governing the Excretion Rate of Urea, J. Biol. Chem. **46**:91, 1921; (*c*) Möller, E.; McIntosh, J. F., and Van Slyke, D. D.: Studies of Urea Excretion: II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, J. Clin. Investigation **6**:427, 1928; (*d*) III. The Influence of Body Size on Urea Output, ibid. **6**:467, 1928.

2. Addis, T., and Drury, D. R.: The Rate of Urea Excretion: VII. Effect of Various Other Factors than Blood Urea Concentration on the Rate of Urea Excretion, J. Biol. Chem. **55**:629, 1923.

3. MacKay, E. M.: Studies of Urea Excretion: V. The Diurnal Variation of Urea Excretion in Normal Individuals and Patients with Bright's Disease, J. Clin. Investigation **6**:505, 1928.

4. Van Slyke, D. D.; Alving, A., and Rose, W. C.: Studies of Urea Excretion: VII. The Effects of Posture and Exercise on Urea Excretion, J. Clin. Investigation **11**:1053, 1932.

5. Bruger, M., and Mosenthal, H. O.: Urea Clearance Test as an Index of Renal Function: I. Studies of Normal Subjects, Arch. Int. Med. **50**:351 (Sept.) 1932; II. The Effect of Ingestion of Carbohydrate (Dextrose), ibid. **50**:359 (Sept.) 1932.

ship between the weight of the kidneys, the area of the body surface and the renal function has been demonstrated by Taylor, Drury and Addis,[6] MacKay and Raulston,[7] MacKay,[8] Addis,[9] Addis, Myers and Oliver[10] and Möller, McIntosh and Van Slyke.[1d] It has been found that the urea clearance and the weight of the kidneys are proportional to the area of the body surface. Addis and Drury[2] and Addis, Barnett and Shevky[11] found that the urea clearance was increased by caffeine and small doses of epinephrine and was decreased by solution of pituitary and large doses of epinephrine. As stated by Peters and Van Slyke,[12] these factors may cause variation in the blood urea clearance either by altering the minute flow of blood through the kidneys or by so influencing the activity of the renal cells that variations occur in the percentage of urea removed from the blood at each passage.

There are comparatively few reports of the employment of the urea clearance test for the determination of renal functional efficiency during pregnancy. Stander, Ashton and Cadden,[13] for four normal women, who were stated to be near term, obtained values ranging from 92 to 110 per cent of the average normal; for three women with "low reserve kidney" the figures ranged from 62 to 122 per cent; for nine with nephritis complicating pregnancy the figures varied from 55.5 to 94 per cent. A more extensive series was studied by Hurwitz and Ohler.[14] For five normal pregnant women they obtained figures of from 83 to 161 per cent; the duration of pregnancy was not stated. Abnormally low values were obtained for fourteen of seventeen women with chronic nephritis, for five with eclampsia and for eight of twenty-one with other forms

6. Taylor, F. B.; Drury, D. R., and Addis, T.: The Regulation of Renal Activity: VIII. The Relation Between the Rate of Urea Excretion and the Size of the Kidneys, Am. J. Physiol. **65**:55, 1923.

7. MacKay, E. M., and Raulston, B. O.: Factors Which Determine Renal Weight; Renal Function, J. Exper. Med. **53**:109, 1931.

8. (*a*) MacKay, E. M.: Comparison of Relation Between Rate of Urea Excretion and Amount of Renal Tissue in Dog and Other Mammals, Am. J. Physiol. **100**:402, 1932; (*b*) Kidney Weight, Body Size and Renal Function, Arch. Int. Med. **50**:590 (Oct.) 1932.

9. Addis, T.: Renal Lesion in Bright's Disease, Am. J. M. Sc. **176**:624, 1928.

10. Addis, T.; Myers, B. A., and Oliver, J.: The Regulation of Renal Activity, Arch. Int. Med. **34**:243 (Aug.) 1924.

11. Addis, T.; Barnett, G. D., and Shevky, A. E.: The Regulation of Renal Activity: I. Regulation of Urea Excretion by the Concentration of Urea in the Blood and in the Urine, Am. J. Physiol. **46**:1, 1918.

12. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry (Interpretations), Baltimore, Williams & Wilkins Company, 1931, p. 350.

13. Stander, H. J.; Ashton, P., and Cadden, J. F.: The Value of the Various Kidney Function Tests in the Differentiation of the Toxemias of Pregnancy, Am. J. Obst. & Gynec. **23**:461, 1932.

14. Hurwitz, D., and Ohler, W. R.: Urea Clearance Test in Toxemias of Pregnancy, J. Clin. Investigation **11**:1119, 1932.

of toxemia of pregnancy. In view of the grave prognostic significance of nephritis occurring as a complication of pregnancy and because of the reliance placed on the urea clearance test in the early detection of renal functional impairment, this study was undertaken to determine whether or not the blood urea clearance in the pregnant state differs from that in the normal nonpregnant state.

The report is based on tests made on forty-seven pregnant women, of whom thirty-nine showed a normal condition, seven had chronic glomerulonephritis and one had myocardial failure. The determinations of urea clearance were made in most cases in the last two months of gestation, the exact time being noted in the tables; as therein indicated, a few determinations were made during the puerperal period. The technic employed in the performance of the test was that advocated by Möller, McIntosh and Van Slyke,[1c] with the exception that, in view of the difficulty of otherwise insuring the complete emptying of the bladder, all specimens of urine were obtained by catheterization. Determinations of urea in the blood and urine were made by the urease-aeration method of Van Slyke and Cullen,[15] the determinations of urea in the blood being made with the Benedict (1932) filtrate. As advocated by Möller, McIntosh and Van Slyke,[1c] the test period was from 8 to 10 a. m. Correction by taking into account the area of the body surface was made according to their suggestion.

EXPERIMENTAL DATA

The detailed findings with regard to the urea clearance test are presented in tables 1 and 4. The thirty-nine patients included in the normal group showed no clinical or laboratory evidence of disease (except the urea clearance findings). The majority of those studied at term had been carefully observed in the antenatal clinic for several months prior to their admission to the hospital. Seven patients in the abnormal group presented definite clinical and laboratory evidence of chronic glomerulonephritis, and one was suffering from myocardial failure, with a moderate degree of generalized edema.

In the normal group, the blood urea clearance, in terms of percentage of the average normal (54 cc., standard clearance and 75 cc., maximum clearance), varied from 28 to 184. As indicated in table 2, there appeared to be a remarkably close relationship between the number of months of pregnancy that had elapsed when the test was made and the urea clearance values, the latter showing a distinct tendency to diminish as the pregnancy progressed. Following delivery, values of 62, 117 and 184 per cent were obtained in three cases. The same rela-

15. Van Slyke, D. D., and Cullen, G. E.: The Determination of Urea by the Urease Method, J. Biol. Chem. **24**:117, 1916.

TABLE 1.—*Urea Clearance in Thirty-Nine Cases of Normal Pregnancy*

Patient	Month of Gestation	Blood Urea N, Mg. per 100 Cc.	Urine Volume, Cc. per Min.	Urea Clearance, Per Cent of Normal
A. D.	3	6.66	0.8	120
A. McG.	4	8.63	0.53	112
E. L.	3	11.11	2.41	110
E. K.	3	8.24	1.1	103
I. S.	5	15.7	0.81	100
	9	11.95	0.56	29
	2 days post partum	8.98	1.1	62
R. S.	5	8.24	0.33	100
A. S.	6	10.27	0.4	100
F. B.	6	11.11	0.56	100
A. C.	6	10.27	0.6	96
J. R.	7	13.33	0.7	90
E. M.	7	14.28	0.56	89
M. R.	7	15.78	0.75	88
D. L.	9	10.79	2.5	88
S. McD.	9	14.49	2.2	87
E. M.	9	13.57	1.36	85
C. E.	9	11.45	1.5	82
A. F.	8	14.7	0.34	79
R. E.	8	8.92	0.37	75
M. G.	9	10.90	0.43	75
A. D.	9	15.87	0.75	74
C. B.	7	13.04	0.6	72
	9	19.35	0.72	66
L. H.	9	16.39	0.31	68
T. P.	9	8.82	0.95	66
H. M.	9	14.18	0.35	66
L. B.	9	10.79	0.45	64
S. B.	9	9.9	0.34	64
N. Di P.	6	15.0	0.69	64
	8	14.28	0.6	61
	9	12.24	1.1	30
L. C.	9	14.42	0.41	61
	2 days post partum	14.28	0.54	117
E. M.	9	9.93	0.7	53
E. M.	9	10.24	0.92	53
M. O.	7	12.39	1.25	50
	9	12.0	0.18	31
R. G.	9	12.29	1.23	50
S. H.	9	10.13	1.15	50
D. J.	9	9.61	0.35	48
B. W.	9	11.32	1.75	46
F. K.	9	11.45	0.76	40
D. K.	9	9.8	0.6	28
A. W.	2 days post partum	9.2	2.08	184
A. K.	9	14.49	0.33	59

TABLE 2.—*Average Values of Urea Clearance in Different Months of Normal Pregnancy*

Month of Gestation	Number of Cases	Urea Clearance, Per Cent of Normal	Average Urea Clearance
3	3	103-120	111
4	1	112	112
5	2	100	100
6	4	64-100	90
7	5	50-90	78
8	3	61-79	72
9	25	28-88	59
Post partum	3	62-184	121

tionship appeared to be maintained in five cases in which determinations were made at different periods in pregnancy, as illustrated in table 3.

In the abnormal group, the urea clearance values ranged from 20 to 51 per cent in the seven patients with chronic glomerulonephritis, and a figure of 70 per cent was obtained for one patient with myocardial failure and generalized edema.

TABLE 3.—*Urea Clearance at Different Periods of Gestation in Five Patients*

Patient	Percentage of Normal at Given Month of Gestation					Percentage of Normal Post Partum
	5	6	7	8	9	
I. S.	100	..	..	..	29	62
C. B.	..	..	72	..	66	..
N. Di P.	..	64	..	61	30	..
L. C.	..	..	..	..	61	117
M. O.	..	..	50	..	31	..

TABLE 4.—*Urea Clearance in Seven Cases of Chronic Glomerulonephritis and One of Myocardial Failure Complicating Pregnancy*

Patient	Month of Gestation	Blood Urea N, Mg. per 100 Cc.	Urine Volume, Cc. per Min.	Urea Clearance, Per Cent of Normal	Condition
E. McC.	4	13.51	0.31	40	Chronic glomerulonephritis
L. D.	Three days post partum	14.15	0.41	40	Chronic glomerulonephritis
E. E.	4½ months after abortion	11.07	0.33	51	Chronic glomerulonephritis
M. G.	8	20.68	0.62	37	Chronic glomerulonephritis
B. W.	6	27.02	0.58	70	Myocardial failure, with generalized edema
T. B.	9	13.21	1.7	27	Chronic glomerulonephritis
L. B.	6	10.6	1.83	20	Chronic glomerulonephritis
E. O'N.	9	7.42	0.42	20	Chronic glomerulonephritis

COMMENT

Möller, McIntosh and Van Slyke [1c] found the lower limit of the normal variation of standard blood urea clearance to be about 75 per cent, and that of maximum clearance to be about 85 per cent of the average normal values. Since practically all the patients in this series had urine volumes of less than 2 cc. per minute, the calculations being made on the basis of the standard clearance formula, 75 per cent may be considered as representing the lower limit of normal for this group. Bruger and Mosenthal [5] stated that single determinations as low as 52 per cent may at times be obtained in normal subjects, but we have never observed this degree of variation in normal persons studied under standard conditions. Our experience is in accord with that of Van Slyke and his associates, who believe that in the majority of instances the most reliable results are obtained if the urea clearance values are interpreted in terms of deviation from the average normal rather than if individual determinations are considered as lying within the probable

range of normal variation. However, in the absence of any other evidence of renal functional impairment, as emphasized by Bruger and Mosenthal,[5] minor variations should not be interpreted dogmatically as absolute values of renal functional efficiency.

If 75 per cent is considered the lower limit of normal for this group of normal pregnant women, twenty patients, or 52.6 per cent, must be considered as showing evidence of renal functional impairment. Values of 50 per cent or less were obtained in nine cases (23.6 per cent). However, as stated previously, in no instance was there any other indication of renal dysfunction, all of the women studied at term passing through an essentially normal labor and puerperal period so far as other than local conditions were concerned. Furthermore, observations showed a gradual decrease in blood urea clearance as pregnancy progressed, with essentially normal findings in the first six to seven months, a rather marked diminution in many cases at term and a sudden increase in the early days of the puerperium. In view of these observations, it is difficult to escape the conviction that the subnormal values which may occur during pregnancy, particularly just prior to the onset of labor, are dependent on factors other than actual renal functional impairment. Our findings are at variance with those of Hurwitz and Ohler,[14] who, in five normal cases, observed no values below 83 per cent, and with those of Stander, Ashton and Cadden,[13] who, in four cases, obtained values of from 93 to 110 per cent. However, their normal cases were obviously too few in number to warrant any definite conclusion, and, particularly in the case of the former, no exact statement was made as to the point in the period of gestation at which the studies were made.

It has long been recognized that normal pregnancy is associated with distinct alterations in protein metabolism and nitrogen balance. The early work of Hagemann,[16] of Jägerroos,[17] of Murlin[18] and of Zacharjewski[19] demonstrated that the early months of pregnancy are associated with a negative, and the latter months, particularly the last two, with a distinctly positive nitrogen balance. As shown by Slemons,[20] during the early days of the puerperium the previously positive nitrogen balance suddenly becomes negative. Occasionally a negative nitrogen balance may be observed during the few days preceding

16. Hagemann, O.: Inaug. Dissert., Berlin, 1891.

17. Jägerroos, B. H.: Studien über den Eiweiss-, Phosphor- und Salzumsatz während der Graviditāt, Arch. f. Gynäk. **66**:517, 1902.

18. Murlin, J. R.: Metabolism of Development: III. Qualitative Effects of Pregnancy on the Protein Metabolism of the Dog, Am. J. Physiol. **28**:422, 1911.

19. Zacharjewski, A. U.: Ueber den Stickstoffwechsel während der letzten Tage der Schwangerschaft und der ersten Tage des Wochenbettes, Ztschr. f. Biol. **12**:368, 1893-1894.

20. Slemons, J. M.: Metabolism in Pregnancy, Johns Hopkins Hosp. Rep. **12**:121, 1904.

delivery, which is probably the result of failing appetite and possibly of beginning catabolic changes, as Stander [21] states. Several observers, including Killian and Sherwin,[22] Caldwell and Lyle,[23] de Wesselow [24] and Stander,[21] have noted a moderate decrease in the concentration of urea in the blood during pregnancy. It has been our experience that the blood urea nitrogen tends to diminish, particularly in the last few months of gestation. Furthermore, Murlin and Bailey [25] found that the relative proportion as well as the absolute amount of urinary urea was diminished in pregnancy, probably as a result of protein retention, which is most marked in the later months.

Other changes occur during pregnancy which may affect the quantitative elimination of urea by the urine. An extremely variable and usually progressively increasing quantity of urea is present in the amniotic fluid. Williams and Bargen [26] found that the concentration of urea nitrogen in the amniotic fluid averaged about 18.25 mg. per hundred cubic centimeters, the total nonprotein nitrogen being about 27.05 mg. per hundred cubic centimeters; similar findings were obtained by Cantarow, Stuckert and Davis.[27] The effect on maternal urea elimination of this accumulation of urea in a fluid of unknown origin can only be conjectured, but it must be accepted as representing an additional point of difference between protein metabolism in the pregnant and in the nonpregnant state.

It is well recognized that the elimination of urea by the urine is influenced by the rate and volume of blood flow through the kidneys. It appears probable that marked alteration in this important function may occur during pregnancy in consequence of the tremendous and progressive increase in the vascularity of the pelvic organs. Finally, another important factor must be taken into consideration, namely, the increase in total and basal metabolism which occurs during the last half of pregnancy. This subject has been carefully studied by a number of investigators, whose work has been summarized by DuBois.[28] The

21. Stander, H. J.: Toxemias of Pregnancy, Medicine **8**:1, 1929.

22. Killian, J. A., and Sherwin, C. P.: Some Chemical Studies in Normal and Abnormal Pregnancies, Am. J. Obst. & Gynec. **2**:6, 1921.

23. Caldwell, W. E., and Lyle, W. G.: The Blood Chemistry in Normal and Abnormal Pregnancy, Am. J. Obst. & Gynec. **2**:17, 1921.

24. de Wesselow, O. L. V.: Some Chemical Observations on the Toxemias of Pregnancy, J. Obst. & Gynaec. Brit. Emp. **29**:21, 1922.

25. Murlin, J. R., and Bailey, H. C.: Further Observations on the Protein Metabolism of Normal Pregnancy, Arch. Int. Med. **12**:288 (Sept.) 1913.

26. Williams, J. L., and Bargen, J. A.: The Uric Acid Content of Human Amniotic Fluid, Am. J. Obst. & Gynec. **7**:406, 1924.

27. Cantarow, A.; Stuckert, H., and Davis, R. C.: The Chemical Composition of Amniotic Fluid: Comparative Study of Human Amniotic Fluid and Maternal Blood, Surg., Gynec. & Obst. **57**:63 (July) 1933.

28. DuBois, E. F.: Basal Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1927.

alteration in basal metabolism results from a number of factors, including the development of the fetus, placenta and uterus, changes in body weight and the increased intra-abdominal pressure which adds to the labor of respiration. A number of observers believe that the increase in the production of heat and in the consumption of oxygen is caused by the growing mass of active protoplasmic tissue (fetal and maternal), and that the maternal production of energy per unit of mass remains unchanged. Rowe and Boyd [29] have recently presented evidence that this is not the case and that, in addition to the factors already mentioned, the excess production of heat is in part dependent on some unknown mechanism engendered by the state of pregnancy. Whatever may be its cause, it is possible that the increase in total metabolism may affect certain factors which enter into the maintenance of the normal elimination of urea, particularly the rate and volume of blood flow through the kidneys.

The concept of the blood urea clearance as a mathematical expression of renal functional activity is based on certain physiologic factors which determine the rate of elimination of urea from the blood under conditions of normal metabolism and blood flow in the nonpregnant state. It seems obvious that alterations in these physiologic factors may occur during pregnancy in view of the profound alterations in protein metabolism and circulation which are associated with that state. Because of the fact that the magnitude of these changes increases progressively throughout the period of gestation, it would appear probable that their effect on the elimination of urea, if they have such an effect, should become more marked in the later months of pregnancy. From our observations of normal pregnant women, we are of the opinion that the end-result of these physiologic changes, particularly the increasing retention of nitrogenous substances, although counteracted to a certain extent by the slightly diminished concentration of urea in the blood, is a diminution in the blood urea clearance values as calculated on the basis of formulas which represent normal conditions in the nonpregnant state. Furthermore, the extreme variability of many of these physiologic changes in different women during pregnancy introduces uncontrollable and variable factors which may render the interpretation of the blood urea clearance findings extremely difficult.

Certain observations made by Goldring [30] may be of significance in this connection. He found that during the acute febrile stage of rheumatic infection the values for blood urea clearance were usually higher than the highest values observed in normal persons, and that

29. Rowe, A. W., and Boyd, W. C.: The Metabolism in Pregnancy: Foetal Influence on Basal Rate, Nutrition **5**:551, 1932.

30. Goldring, W.: Studies on the Kidney in Acute Infection: II. Observations with the Urea Clearance Test in Acute Rheumatic Infection, J. Clin. Investigation **10**:345, 1931.

during the afebrile convalescent period the values were usually lower than the lowest observed normal values, returning to normal within about two weeks. These findings were interpreted as indicating a state of renal hyperfunction during the acute stage, as a response to the demand for increased protein catabolism, and a state of renal hypofunction during the convalescent period, probably a result of toxic injury to the renal parenchyma. Whereas this interpretation may be correct, it is also possible that the subnormal values obtained during the period of convalescence may be in some way related to the state of positive nitrogen balance and protein storage which usually follows the prolonged state of negative balance and increased protein catabolism associated with febrile disorders. The condition during convalescence would in this respect be analogous to that which exists during the later months of gestation, that during the acute febrile period being analogous to the first few months of pregnancy and the first few days of the puerperium. Interpreted on this basis, our observations during these periods coincide with those of Goldring,[30] this coincidence suggesting the validity of the concept, particularly in view of the fact that his interpretation of the low clearance values during convalescence was apparently not supported by the presence of either clinical or laboratory evidence of renal disease. It seems unlikely that renal dysfunction dependent on an organic renal lesion occurring as a result of prolonged acute infection would consistently fail to manifest itself by some change in the urinary findings.

On the basis of our observations, we feel that the value of the urea clearance test as an accurate index of renal functional efficiency in pregnancy diminishes as the period of gestation lengthens. Subnormal values obtained during the last two months of pregnancy must be interpreted with extreme caution, particularly in the absence of clinical or laboratory evidence of renal functional insufficiency. Investigation of physiologic alterations in protein metabolism and in the rate and volume of blood flow through the kidneys during this period, as well as of the altered relationship between the area of the maternal body surface and the urea elimination, may throw some light on the factors directly responsible for the observed difference between urea clearance in the pregnant and in the nonpregnant state.

SUMMARY

1. Determinations of urea clearance were made in thirty-nine cases of normal pregnancy and in seven cases of chronic glomerulonephritis and one of myocardial failure complicating pregnancy.

2. In the normal group, the urea clearance values ranged from 28 to 184 per cent of the average normal as established by Van Slyke and his associates.

3. The urea clearance, which was normal in the first few months of gestation, diminished as pregnancy progressed, being rather consistently low a few days before the onset of labor. High values were obtained during the early days of the puerperal period.

4. It is suggested that these findings may be dependent on changes in total metabolism and protein metabolism, fetal development and alterations in the rate and volume of blood flow through the kidneys.

5. It is further suggested that the laws governing the elimination of urea in the nonpregnant state, which form the basis of the mathematical calculation of the blood urea clearance, may not apply to the pregnant state because of the physiologic changes mentioned.

6. Subnormal clearance values obtained during the last two months of gestation must be interpreted with extreme caution, particularly in the absence of clinical or laboratory evidence of renal dysfunction.

Book Reviews

The Technique of Using Paper Films for Roentgenograms of the Chest. By M. W. Barnard, M.D.; J. B. Amberson, Jr., M.D., and M. F. Loew, M.D., American Review of Tuberculosis **25**:752 (June) 1932. By M. W. Barnard, M.D., Quarterly Bulletin, The Milbank Memorial Fund **10**: (April) 1932. By J. B. Amberson, Jr., M.D.; M. W. Barnard, M.D., and M. F. Loew, M.D., Transactions of Twenty-Eighth Annual Meeting of the National Tuberculosis Association, 1932.

A review of the investigative work of Amberson, Barnard and Loew on the comparative value of paper and of celluloid films for roentgenograms of the chest leads one to the following conclusions.

The present financial condition has made economic demands, and necessarily workers using the x-rays have been trying to find a suitable substitute for the rather expensive celluloid x-ray film.

The substitute must be of low cost but still compare favorably with the more expensive accepted celluloid film.

The use of a single coated paper is not new; from time to time manufacturers have sold x-ray paper, but the quality has not been satisfactory except for the examination of small parts. Recently manufacturers have brought out an improved paper, and at present many of the large hospitals and clinics are using this paper, especially for follow-up examinations.

The present paper compares quite favorably with the celluloid film, even in the examination of heavier parts, such as the chest and stomach. The application of the paper in examinations of the chest, according to the authors, has been quite satisfactory. They have recently examined 1,000 cases, using both the paper and the celluloid film. The celluloid film always afforded somewhat better clarity and detail, but for diagnostic purposes the two films were in substantial agreement. The authors give a résumé of their cases with comments.

The small pulmonary findings are more apt to be missed when the paper film is used, but the cheapness of the examination makes future check ups economical.

There are difficulties in manufacturing the paper which lead to slight variations in the photosensitiveness of different batches of paper. (The same variations are often encountered with celluloid films.)

Paper films do not produce as clear roentgenograms as do celluloid films. The difference is not sufficient to impair the value of the paper for practical purposes. The slight diagnostic error is offset by the possibility of examining and reexamining large groups economically. The smaller expense ($1.25 per celluloid film against $0.40 per paper film) makes the roentgen examination of large groups of school children possible.

La constipation: Comment l'éviter? Comment la guérir? By Victor-Pauchet and H. Gaehlinger. With a Preface by Prof. P. Carnot. Second edition. Paper. Price, 38 francs. Pp. 214, with 8 figures. Paris: Gaston Doin & Cie, 1933.

This book, now in its second edition, is an inclusive summary of the art of treating the constipated patient; it contains a systematic review of possible causes of constipation, with descriptions of treatment by medicine, hydrotherapy, physical therapy and surgical measures. Since the book is apparently not intended to be scientific, one cannot complain of features which would otherwise be objectionable; these include the absence of clinical or experimental proof of important assumptions, the lack of a bibliography and index, the uncritical repetition of such statements as the one that "savages defecate three times a day," and the unneces-

sarily unctuous descriptions of a mineral water as "highly mineralized" and "rich in chlorides." The section on surgical treatment sketches briefly a repertory of ectomies, pexies and plicatures for the technical details of which the reader is referred to another work, and mention is made of methods of intestinal antisepsis and vaccination; the absence of specific facts and case histories leaves this section unconvincing. On other points, however, the book contains concisely worded practical suggestions which may be of help in dealing with difficult cases.

L'exploration de l'intestin: Diagnostic et traitement des maladies et des syndromes. By R. Morichau-Beauchant. Paper. Price, 42 francs. Pp. 514, with 1 figure. Paris: Gaston Doin & Cie, 1933.

The purpose of this book is to summarize for students and practicing physicians the diagnosis and treatment of disorders of the intestine, and necessarily includes the differential diagnosis of practically all acute and chronic abdominal conditions. In the first of its four parts it deals with methods of examination; in the second, with diagnosis and treatment of diseases and syndromes; in the third, with acute surgical intestinal conditions, and in the fourth, with acute painful nonintestinal conditions. Occasional lack of specific factual detail gives the book an air of superficiality despite its length, and most students would prefer to see an alphabetical index replace part of the twenty-one page table of contents which is placed at the end of the book. Nevertheless, one feels that the author has done commendable work with so great a mass of material and that he achieves his purpose.

Diet in Sinus Infections and Colds. By Egon V. Ullmann. Price, $2. Pp. 116. New York: The Macmillan Company, 1933.

This book, which is prepared apparently for the layman, judging from the elementary language in which it is written, has to do with the implied importance of diet in the prevention and treatment of sinus infections and colds, predicating at first the dietetic treatment of these conditions on the work that has been done in the past in regard to the lack of resistance to infection in the absence of certain vitamins in the diet. The author, however, uses these known facts to slight extent, and bases his concept of the treatment of sinus infection largely on a so-called diet from which salt has been withdrawn. The reviewer knows of no scientific evidence to show that acidosis is responsible for infection or that increasing the body calcium and decreasing the chloride will affect infections of the nature of colds and sinus disorders. The book falls into the category of fadism, based on a minimum of scientific proof.

The Vitamins in Health and Disease. By Barnett Sure. Price, $2. Pp. 206. Baltimore: Williams & Wilkins Company, 1933.

This book, written in a pleasant and authoritative manner, deals systematically with the vitamins along conventional lines. Although the book is well up to date, it must be admitted that little is added to what is already easily available in monographic form. The lengthy table of the vitamin contents of various foods is useful, and the final chapter on clinical applications will appeal to practicing physicians. For the statement on the jacket that "Vitamin deficiency often spells the difference between . . . catching everything that comes along and enjoying freedom from infection," we trust the author is not responsible.